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A SPECIAL MEETING REVIEW EDITION

Highlights in Lymphoma From the 2016 American Society of Hematology Annual Meeting and Exposition

A Review of Selected Presentations From the 2016 American Society of Hematology Annual Meeting and Exposition December 3-6, 2016 • San Diego, California

Special Reporting on:

- Brentuximab Vedotin Demonstrates Significantly Superior Clinical Outcomes in Patients With CD30-Expressing Cutaneous T Cell Lymphoma Versus Physician's Choice (Methotrexate or Bexarotene): The Phase 3 ALCANZA Study
- Obinutuzumab-Based Induction and Maintenance Prolongs Progression-Free Survival (PFS) in Patients With Previously Untreated Follicular Lymphoma: Primary Results of the Randomized Phase 3 GALLIUM Study
- Preliminary Results From a Phase 1/2 Study of Brentuximab Vedotin in Combination With Nivolumab in Patients With Relapsed or Refractory Hodgkin Lymphoma
- BEACOPP Escalated Followed by Radiotherapy of Initial Bulk or Residual Disease in Advanced Stage Hodgkin Lymphoma: Long-Term Follow Up of the HD9 and HD12 Trials of the German Hodgkin Study Group
- A Phase I Study With an Expansion Cohort of the Combination of Ipilimumab and Nivolumab and Brentuximab Vedotin in Patients With Relapsed/Refractory Hodgkin Lymphoma: A Trial of the ECOG-ACRIN Cancer Research Group (E4412 Arms D and E)
- Five-Year Survival Data From a Pivotal Phase 2 Study of Brentuximab Vedotin in Patients With Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma
- CheckMate 205 Update With Minimum 12-Month Follow Up: A Phase 2 Study of Nivolumab in Patients With Relapsed/Refractory Classical Hodgkin Lymphoma

PLUS Meeting Abstract Summaries

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ON THE WEB:
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Indication

ADCETRIS is indicated for the treatment of patients with classical HL at high risk of relapse or progression as post autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation.

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 (PN):** ADCETRIS treatment causes a PN that is predominantly sensory. Cases of motor PN have also been reported. ADCETRIS-induced PN 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. Patients who 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 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 ≥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 ≥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 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

Her remission means the world to her.

PROTECT IT.

In the post auto-HSCT consolidation treatment of patients with classical Hodgkin lymphoma (HL) at high risk of relapse or progression, ADCETRIS® (brentuximab vedotin) significantly increased PFS compared to placebo[1]

18.8

month median PFS benefit[1]

ADCETRIS: 42.9 months (95% CI: 30.4, 42.9†)

Placebo: 24.1 months (95% CI: 11.5, NE)

HR=0.57 (95% CI: 0.40, 0.81) *P*=0.001

NE=Not estimable. †Estimates are unreliable.

STUDY DESIGN: ADCETRIS was evaluated as post auto-HSCT consolidation treatment in a multicenter, randomized, double-blind, placebo-controlled trial of 329 patients aged ≥18 years with classical Hodgkin lymphoma (histologically confirmed) at high risk of relapse or disease progression within 30-45 days post auto-HSCT. Patients were randomized to receive ADCETRIS 1.8 mg/kg (n=165) or placebo (n=164) q3w for up to 16 cycles. High risk of relapse/progression was defined by ≥1 of the following risk factors: refractory disease, relapse <12 months after frontline therapy, relapse ≥12 months with extranodal disease. Primary endpoint was PFS per independent review facility.[1,2]

The most common adverse reactions (≥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[1]

Visit ADCETRISpro.com to learn more.

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.
- **Gastrointestinal (GI) complications:** Fatal and serious GI complications, including perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, neutropenic colitis, and ileus, have been reported in ADCETRIS-treated patients. Lymphoma with preexisting GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, perform a prompt diagnostic evaluation and treat appropriately.
- **Embryo-fetal toxicity:** Based on the mechanism of action and findings in animals, ADCETRIS can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Adverse Reactions:

The most common serious adverse reactions in the ADCETRIS-treated arm, regardless of causality, were pneumonia, pyrexia, vomiting, nausea, hepatotoxicity, and peripheral sensory neuropathy.

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.

Advise females of reproductive potential to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Advise males with female sexual partners of reproductive potential to use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Advise patients to report pregnancy immediately and avoid breastfeeding while receiving ADCETRIS.

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

References: 1. ADCETRIS [Prescribing Information]. Bothell, WA: Seattle Genetics, Inc.; March 2016. **2.** Moskowitz CH, Nademanee A, Masszi T, et al; for the AETHERA Study Group. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2015;385:1853-1862.

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CD30-DIRECTED

ADCETRIS®

brentuximab vedotin | for injection

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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

ADCETRIS is a CD30-directed antibody-drug conjugate indicated for the treatment of patients with classical Hodgkin Lymphoma (HL) at high risk of relapse or progression as post-auto-HSCT consolidation.

DOSAGE AND ADMINISTRATION

Dosage Recommendations

Administer ADCETRIS as an intravenous infusion over 30 minutes every 3 weeks.

For classical HL post-auto-HSCT consolidation treatment, initiate ADCETRIS treatment within 4-6 weeks post-auto-HSCT or upon recovery from auto-HSCT. These patients should continue treatment until a maximum of 16 cycles, disease progression, or unacceptable toxicity.

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 (PN)

ADCETRIS treatment causes a PN that is predominantly sensory. Cases of motor PN have also been reported. ADCETRIS-induced PN 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 PN 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 monomethyl auristatin E (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.

Gastrointestinal (GI) Complications

Fatal and serious GI complications including perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, neutropenic colitis, and ileus have been reported in ADCETRIS-treated patients. Lymphoma with preexisting GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, perform a prompt diagnostic evaluation and treat appropriately.

Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, ADCETRIS can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of ADCETRIS in pregnant women. Brentuximab vedotin caused embryo-fetal toxicities, including significantly decreased embryo viability and fetal malformations, in animals at maternal exposures that were similar to the clinical dose of 1.8 mg/kg every 3 weeks. Advise females of reproductive potential to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS. If ADCETRIS is used during pregnancy or if the patient becomes pregnant during ADCETRIS treatment, the patient should be apprised of the potential risk to the fetus.

ADVERSE REACTIONS

Clinical Trial Experience

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.

In a placebo-controlled trial of ADCETRIS in 329 patients with classical HL at high risk of relapse or progression post-auto-HSCT, the most common adverse reactions (≥20%) in the ADCETRIS-treatment arm, regardless of causality, were neutropenia, peripheral sensory neuropathy, thrombocytopenia, anemia, upper respiratory tract infection, fatigue, peripheral motor neuropathy, nausea, cough, and diarrhea. The most common adverse reactions occurring in at least 10% of patients, using the NCI CTC Version 4, are shown in Table 1.

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

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 jiroveci 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).

Table 1: Most Commonly Reported (≥10% in the ADCETRIS arm) Adverse Reactions in Study 3

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

Gastrointestinal disorders:

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

Hepatobiliary disorders: hepatotoxicity.

Infections: PML, serious infections and opportunistic infections.

Metabolism and nutrition disorders: hyperglycemia.

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 in 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

Risk Summary

ADCETRIS can cause fetal harm based on the findings from animal studies and the drug's mechanism of action. In animal reproduction studies, administration of brentuximab vedotin to pregnant rats during organogenesis at doses similar to the clinical dose of 1.8 mg/kg every three weeks caused embryo-fetal toxicities including congenital malformations. Consider the benefits and risks of ADCETRIS and possible risks to the fetus when prescribing ADCETRIS to a pregnant woman.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

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 (≥99%), post-implantation loss (≥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.

Lactation

There is no information regarding the presence of brentuximab vedotin in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed infant from ADCETRIS, including cytopenias and neurologic or gastrointestinal toxicities, advise patients that breastfeeding is not recommended during ADCETRIS treatment.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating ADCETRIS therapy.

Contraception

Females

Advise females of reproductive potential to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS. Advise females to immediately report pregnancy.

Males

ADCETRIS may damage spermatozoa and testicular tissue, resulting in possible genetic abnormalities. Males with female sexual partners of reproductive potential should use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Infertility

Males

Based on findings in rats, male fertility may be compromised by treatment with ADCETRIS.

Pediatric Use

Safety and effectiveness of ADCETRIS have not been established in pediatric 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.

Renal Impairment

Avoid the use of ADCETRIS in patients with severe renal impairment (CLcr <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 (CLcr >50-80 mL/min; n=4), moderate (CLcr 30-50 mL/min; n=3) and severe (CLcr <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, ≥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 and severe hepatic impairment, the rate of ≥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.

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.

• Gastrointestinal Complications

Advise patients to contact their health care provider if they develop severe abdominal pain, chills, fever, nausea, vomiting, or diarrhea.

• Females and Males of Reproductive Potential

ADCETRIS can cause fetal harm. Advise women receiving ADCETRIS to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Advise males with female sexual partners of reproductive potential to use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Advise patients to report pregnancy immediately.

• Lactation

Advise patients to avoid breastfeeding while receiving ADCETRIS.

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Clinical Advances in
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Brentuximab Vedotin Demonstrates Significantly Superior Clinical Outcomes in Patients With CD30-Expressing Cutaneous T Cell Lymphoma Versus Physician's Choice (Methotrexate or Bexarotene): The Phase 3 ALCANZA Study

Cutaneous T-cell lymphoma (CTCL) is incurable with current therapies, and advanced-stage disease is associated with a poor prognosis. Standard-of-care therapies, such as methotrexate and bexarotene, rarely provide durable responses.[1,2] The cell surface marker CD30 is commonly expressed on malignant T cells of mycosis fungoides and primary cutaneous anaplastic large cell lymphoma (ALCL). Brentuximab vedotin is an antibody-drug conjugate consisting of an anti-CD30 monoclonal antibody attached by a protease-cleavable linker to monomethyl auristatin E, a microtubule disrupting agent.[3] In two phase 2 studies of patients with CTCL, brentuximab vedotin showed an acceptable safety profile and significant clinical activity, with objective response rates (ORRs) of approximately 70%.[4,5]

The randomized, open-label, phase 3 ALCANZA trial (A Phase 3 Trial of Brentuximab Vedotin [SGN-35] Versus Physician's Choice [Methotrexate or Bexarotene] in Patients With CD30-Positive Cutaneous T-Cell Lymphoma) evaluated brentuximab vedotin (1.8 mg/kg every 3 weeks) vs physician's choice of methotrexate (5-50 mg weekly) or bexarotene (300 mg/m^2 daily) in patients with previously treated CD30-positive mycosis fungoides or primary cutaneous ALCL.[6] Patients were treated for up to sixteen 21-day cycles; among those receiving methotrexate or bexarotene, the goal was to achieve the maximum tolerated dose.

Patients were recruited from 52 centers in 13 countries. Enrolled patients were required to have expression of CD30 on at least 10% of either neoplastic cells or lymphoid infiltrate by central review of biopsy. Two biopsies were required for patients with mycosis fungoides. All mycosis fungoides patients had received at least 1 prior systemic therapy, and all primary cutaneous ALCL patients had received prior radiotherapy or at least 1 prior systemic therapy. The primary endpoint was the rate of objective response lasting at least 4 months (ORR4), with results assessed by independent review of global response using consensus guidelines published by the International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer.[7] ORR4 was chosen as the primary endpoint in order to capture response rate and duration in a single measurement. Global response is a composite of skin evaluation, radiographic assessment, and Sézary cell enumeration. Secondary endpoints included progression-free survival (PFS), the rate of complete response (CR), and symptom burden as measured by the symptom domain of the Skindex-29 quality-of-life tool.[8]

The study randomly assigned 66 patients to the brentuximab vedotin arm and 65 to the comparator arm. Data from 64 patients in each arm were available for the intent-to-treat analysis. Baseline characteristics were generally well-balanced between the 2 arms. Patients had a median age of 59 to 62 years (range, 22-83 years), 52% to 58% were male, and nearly all patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. Baseline biopsies showed a median baseline

ABSTRACT SUMMARY Four-Year Survival and Durability Results of Brentuximab Vedotin in Combination With CHP in the Frontline Treatment of Patients With CD30-Expressing Peripheral T-Cell Lymphomas

A phase 1 trial evaluated 6 cycles of brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisone followed by 10 cycles of brentuximab vedotin monotherapy as first-line treatment in 26 patients with peripheral T-cell lymphoma (Abstract 2993). Most of the patients (73%) had systemic ALCL, and most (73%) had stage III/IV disease. After a median observation time of 53 months (range, 4.6-58.3 months), 17 patients remained in the study. An AE led 23% of patients to discontinue study treatment. The most common grade 3/4 AEs were febrile neutropenia (31%), nonfebrile neutropenia (23%), anemia (15%), and pulmonary embolism (12%). Peripheral neuropathy was reported in 73% of patients, but resolved in most (with a median time to resolution of 5 months). No deaths occurred within 30 days of cessation of study treatment. The estimated 4-year PFS was 53% (95% CI, 31%-69%), and the estimated 4-year OS was 80% (95% CI, 59%-91%).

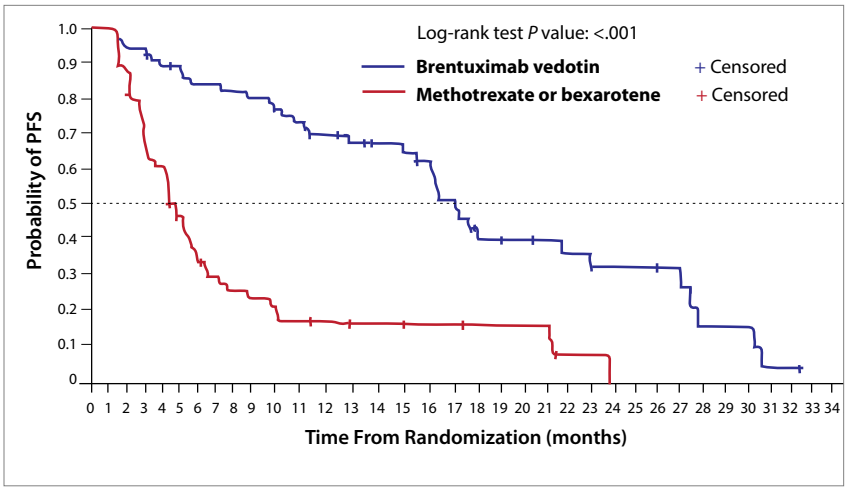

Figure 1. Progression-free survival (PFS) in the phase 3 ALCANZA trial. ALCANZA, A Phase 3 Trial of Brentuximab Vedotin (SGN-35) Versus Physician's Choice (Methotrexate or Bexarotene). Adapted from Kim YH et al. ASH abstract 182. *Blood*. 2016;128(suppl 22).[6]

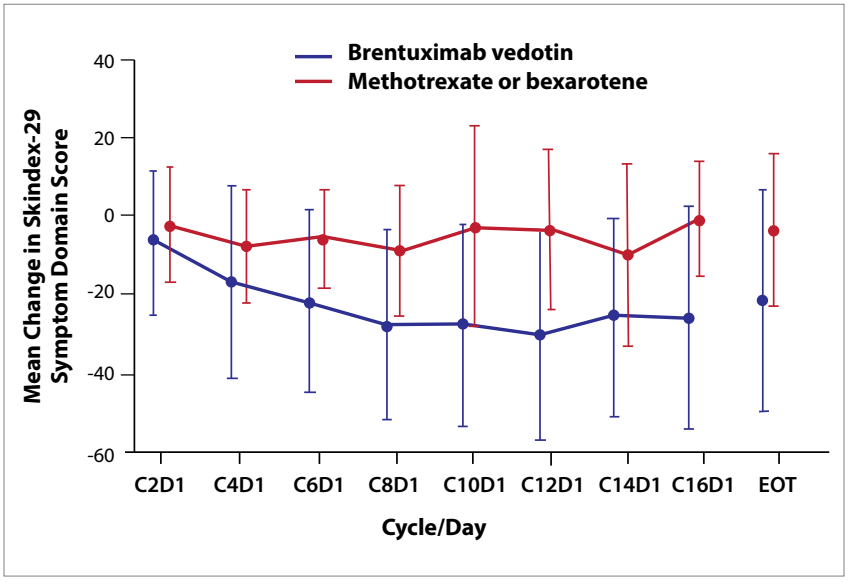

Figure 2. In the phase 3 ALCANZA trial, brentuximab vedotin provided a superior reduction in skin symptoms. ALCANZA, A Phase 3 Trial of Brentuximab Vedotin (SGN-35) Versus Physician's Choice (Methotrexate or Bexarotene); C, cycle; D, day; EOT, end of treatment. Adapted from Kim YH et al. ASH abstract 182. *Blood*. 2016;128(suppl 22).[6]

CD30 expression level of 31% to 33% (range, 3%-100%). Patients had received a median of 4 prior therapies overall (range, 0-15), and a median of 2 prior systemic therapies (range, 0-11). Approximately three-fourths of patients in each arm had mycosis fungoides, of whom 61% to 67% had advanced disease. In the brentuximab vedotin arm, 25% of patients had primary cutaneous ALCL vs 23% in the comparator arm. The brentuximab vedotin arm had a larger proportion of primary cutaneous ALCL patients with extracutaneous disease (44% vs 27%).

Median treatment duration was 36 weeks with brentuximab vedotin, 17 weeks with bexarotene, and 9 weeks with methotrexate. After a median follow-up of 17.5 months, the trial demonstrated a significant improvement in ORR4 with brentuximab vedotin vs physician's choice of treatment (56.3% vs 12.5%; $P<.0001$). Brentuximab vedotin yielded a CR rate of 15.6% vs 1.6% in the comparator arm ($P=.0046$), and the PFS was 16.7 months vs 3.5 months, respectively (HR, 0.270; 95% CI, 0.169-0.430; $P<.0001$; Figure 1). Brentuximab vedotin provided a superior reduction in skin symptoms, as assessed by Skindex-29 symptom domain scores (-27.96 points vs -8.62 points; $P<.0001$; Figure 2). In the brentuximab vedotin arm, responses were observed across all stages of disease. Brentuximab vedotin was superior in subset analyses, demonstrating improved ORR4 in subgroups based on ECOG PS, sex, age, mycosis fungoides vs primary cutaneous ALCL, involvement of skin only vs other areas, and baseline tumor score.

The safety profile associated with brentuximab vedotin was generally similar to that observed in previous trials. An adverse event (AE) of grade 3 or higher was observed in 41% of the brentuximab vedotin arm vs 47% of the physician's choice arm. A serious AE occurred in 29% of patients in each arm. AEs resulting in discontinuation of study treatment occurred in 24% vs 8% of patients, respectively. In the brentuximab vedotin arm, 6% of patients died within 30 days of the last dose vs 0 patients in the comparator arm. Among the 4 patients who died in the brentuximab vedotin arm, 3 died from causes considered unrelated to study treatment: lymphoma progression, pulmonary embolism, and sepsis. One patient with primary cutaneous ALCL died from multiple organ dysfunction syndrome attributed to tumor necrosis at visceral disease sites caused by brentuximab vedotin. The

most common treatment-emergent AE of any grade was peripheral neuropathy, occurring in 67% of brentuximab vedotin patients vs 6% of patients receiving methotrexate or bexarotene, followed by nausea (36% vs 13%) and diarrhea (29% vs 6%). No grade 4 peripheral neuropathy was reported in the brentuximab vedotin arm. After a median 22.9 months of follow-up, peripheral neuropathy had improved or resolved in 82% of affected patients receiving brentuximab vedotin.

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Obinutuzumab-Based Induction and Maintenance Prolongs Progression-Free Survival (PFS) in Patients With Previously Untreated Follicular Lymphoma: Primary Results of the Randomized Phase 3 GALLIUM Study

Follicular lymphoma is considered incurable, and patients usually present with advanced disease at diagnosis.[1,2] Median PFS for patients with advanced symptomatic follicular lymphoma is 6 to 8 years, and median survival is at least 12 years. Rituximab, an anti-CD20 monoclonal antibody, is a component of follicular lymphoma therapy during induction and maintenance and has played a key role in extending survival.[3] Obinutuzumab (GA101) is a glycoengineered, humanized, type II, anti-CD20 monoclonal antibody that has demonstrated increased induction of direct cell death and antibody-directed cellular cytotoxicity, with reduced dependency on complement.[4] Glycoengineering of the Fc region of the antibody was undertaken with the goal of enhancing immune effector functions.[5] The glycoengineered antibody also showed a slower rate of internalization upon binding to SU-DHL4 cells and from cells in whole blood obtained from patients with chronic lymphocytic leukemia. In phase 2 clinical trials, obinutuzumab combined with lenalidomide or chemotherapy demonstrated activity in previously treated patients with follicular lymphoma or indolent non-Hodgkin lymphoma (NHL).[6,7]

The international, open-label, phase 3 GALLIUM study (A Study of Obinutuzumab [RO5072759] Plus Chemotherapy in Comparison With MabThera/Rituxan [Rituximab] Plus Chemotherapy Followed by GA101 or MabThera/Rituxan Maintenance in Patients With Untreated Advanced Indolent Non-Hodgkin's Lymphoma) evaluated obinutuzumab plus chemotherapy vs rituximab plus chemotherapy in patients with treatment-naive, indolent B-cell NHL. Dr Robert Marcus presented results for 1202 patients with previously untreated follicular lymphoma of grade 1 to 3a.[8] Patients had stage III/IV disease or bulky stage II disease, defined by a tumor diameter of at least 7 cm. All patients received induction chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); cyclophosphamide, vincristine, and prednisone (CVP); or bendamustine. In addition, patients were randomly assigned to receive treatment with either obinutuzumab or rituximab. Obinutuzumab (1000 mg) was administered on days 1, 8, and 15 of cycle 1. Thereafter, it was administered on day 1 of cycles 2 to 8 in patients receiving 3-week cycles of CHOP or CVP or

on day 1 of cycles 2 to 6 in patients receiving 4-week cycles of bendamustine. Rituximab (375 mg/m^2) was administered on day 1 of cycles 1 to 8 in patients receiving 3-week cycles of CHOP or CVP or on day 1 of cycles 1 to 6 in patients receiving 4-week cycles of bendamustine.

After induction, patients who achieved a CR or partial response (PR) continued to receive the same antibody treatment every 2 months as maintenance therapy. The study had an 80% power to detect a hazard ratio (HR) of 0.74 in follicular lymphoma patients. The primary endpoint was investigator-assessed PFS in follicular lymphoma patients. A preplanned interim efficacy analysis demonstrated a superior PFS in the obinutuzumab arm. As a result, the study was unblinded as recommended by the independent data monitoring committee, with a data cutoff of January 31, 2016.

At the end of induction, the ORR based on investigator assessment was 86.9% in the rituximab arm vs 88.5% in the obinutuzumab arm. CR rates were 23.8% vs 19.5%, respectively. After a median follow-up of 34.5 months, 3-year PFS was estimated at 73.3% with rituximab vs 80.0% with obinutuzumab, reflecting a 33% reduction in the risk of progression or death in patients treated with obinutuzumab (HR, 0.66; 95% CI, 0.51-0.85; *P*=.0012; Figure 3). PFS as assessed by an independent review committee confirmed obinutuzumab superiority (HR, 0.71; 95% CI, 0.54-0.93; *P*=.014). No significant difference was observed in overall survival (OS; *P*=.21). Discontinuation rates were 14.2% for patients receiving rituximab vs 16.3% for patients receiving obinutuzumab.

AEs of grade 3 or higher were observed in 67.9% of patients in the rituximab arm vs 74.9% of patients in the obinutuzumab arm, and included neutropenia in 37.9% vs 43.9%. Grade 3/4 febrile neutropenia occurred in 4.9% vs 6.9% of patients, respectively. Other grade 3/4 AEs of interest that were more frequent in the obinutuzumab arm included infections (15.6% vs 20.0%) and infusion-related reactions (6.7% vs 12.4%). Serious AEs were also more frequent with obinutuzumab (39.9% vs 46.1%). The rate of death was higher overall than anticipated (3.4% with rituximab vs 4.0% with obinutuzumab). In both treatment arms, the use of bendamustine was associated with a higher rate of death (5%) than CHOP or CVP.

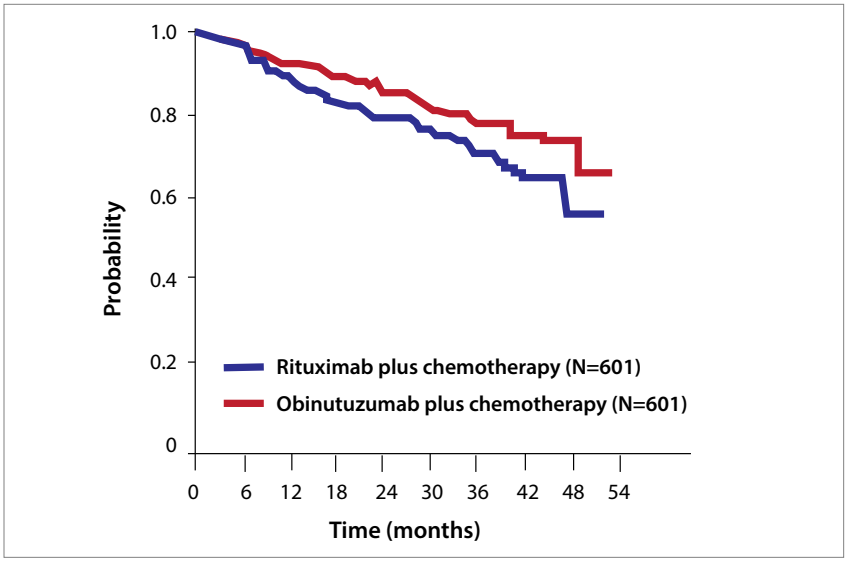

Figure 3. Progression-free survival among patients with follicular lymphoma in the phase 3 GALLIUM study. GALLIUM, A Study of Obinutuzumab [RO5072759] Plus Chemotherapy in Comparison With MabThera/Rituxan (Rituximab) Plus Chemotherapy Followed by GA101 or MabThera/Rituxan Maintenance in Patients With Untreated Advanced Indolent Non-Hodgkin's Lymphoma. Adapted from Marcus R et al. ASH abstract 6. *Blood*. 2016;128(suppl 22).[8]

ABSTRACT SUMMARY Phase III Randomized Study of R-CHOP Versus DA-EPOCH-R and Molecular Analysis of Untreated Diffuse Large B-Cell Lymphoma: CALGB/Alliance 50303

The Alliance Intergroup compared rituximab plus CHOP (R-CHOP) vs dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin plus rituximab (EPOCH-R) in patients with stage 2 or higher, newly diagnosed DLBCL (Abstract 469). The study was initiated in 2005. The efficacy analysis provided data for 233 patients in the R-CHOP arm and 232 patients in the dose-adjusted EPOCH-R arm. The baseline demographics and disease characteristics were well-balanced. Approximately 75% of patients had stage 3 or 4 disease. There were no significant differences in response between the 2 treatments. Overall response rates were approximately 89% in each arm. CR rates were 62% for R-CHOP vs 61% for dose-adjusted EPOCH-R. Event-free survival and OS did not significantly differ between the groups. More toxicity was seen with dose-adjusted EPOCH-R. Patients in this arm were more likely to discontinue treatment early (6.5% vs 1.5%; *P*=.004).

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Preliminary Results From a Phase 1/2 Study of Brentuximab Vedotin in Combination With Nivolumab in Patients With Relapsed or Refractory Hodgkin Lymphoma

In Hodgkin lymphoma (HL), cure rates of 80% are achieved by combining chemotherapy and radiation treatments.[1,2] However, long-term toxicities, such as secondary malignancies and cardiovascular effects, remain a concern.[1,2] In a phase 2 study of 102 HL patients with relapsed or refractory disease following autologous stem cell transplant (SCT), durable remissions were achieved after treatment with brentuximab vedotin.[3] Among the 34 patients who achieved a CR with brentuximab vedotin, 16 (47%) remained progression-free after a median follow-up of 53 months. Nivolumab is a fully human monoclonal antibody that targets the programmed death 1 (PD-1) immune checkpoint pathway. PD-1 is expressed on T cells and serves as a checkpoint to limit the immune responses mediated by these cells. Tumor cells that express the PD ligands 1 (PD-L1) or 2 (PD-L2) inhibit the surveillance activity of T cells, thus allowing the tumor cells to evade immune detection. Classical HL is marked by the presence of malignant Reed-Sternberg cells surrounded by ineffective inflammatory and immune cells. PD-L1 and PD-L2 expression is often increased on Reed-Sternberg cells, and nivolumab yielded an ORR of 87% and acceptable tolerability in a study of 23 heavily pretreated patients with relapsed or refractory HL.[4] In a single-arm, phase 2 trial of 80 HL patients whose disease had failed to respond to both autologous SCT and treatment with brentuximab vedotin, nivolumab monotherapy was associated with an ORR of 66%, including a 28% CR rate.[5]

A phase 1/2 study evaluated the safety and efficacy of brentuximab vedotin plus nivolumab in adults with HL whose disease had failed to respond to first-line therapy.[6] Patients were excluded from this study if they had previously received more than 1 line of prior therapy; therapy with brentuximab vedotin; treatment with any agent that targets the pathways for PD-1, cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), or CD137; or autologous SCT. Patients received treatment with the 2 antibodies in 21-day cycles for a maximum of 4 cycles. During cycle 1, brentuximab vedotin (1.8 mg/kg) was administered on day 1 and nivolumab (3 mg/kg) was administered on day 8. Thereafter, both drugs were administered on day 1 of each cycle. After completion of the final response assessment, patients were allowed to undergo autologous SCT. Investigator assessment of lymphoma response and progression was based on the Lugano Classification Revised Staging System for malignant lymphoma.[7]

The study enrolled 42 patients, with a median age of 37 years. Forty percent of patients had primary refractory disease, 33% had relapsed after a remission lasting no longer than 1 year, and 26% had relapsed after a remission duration of longer than 1 year. Twenty-six percent of patients had extranodal disease, and 10% had bulky disease. In 88% of patients, first-line therapy consisted of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), and 12% had previously received radiation. At the time the study was reported, all patients had received at least 1 dose of the study drugs, 29% remained on treatment, and 67% had completed treatment.

The ORR in 29 evaluable patients was 90%, including a CR rate of 62% (Figure 4). Among the 18 patients who achieved a CR, 14 had a Deauville

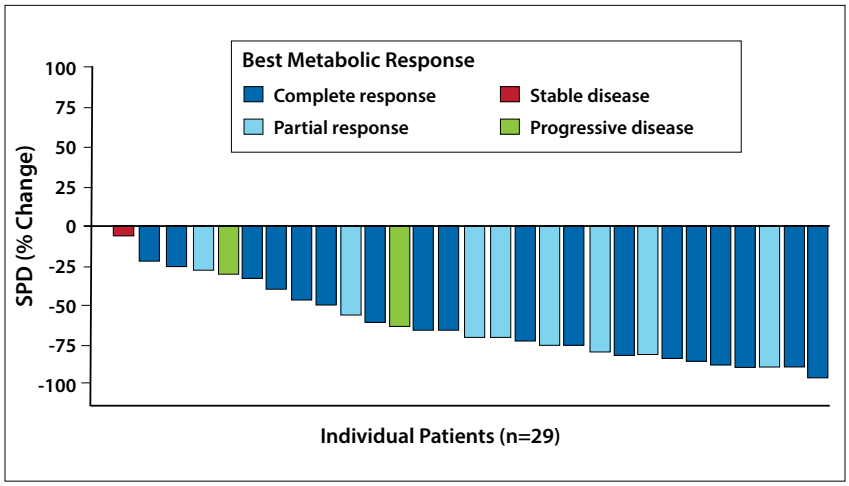

Figure 4. Overall response in a phase 1/2 study of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. SPD, sum of the products of the greatest perpendicular diameters. Adapted from Herrera AF et al. ASH abstract 1105. *Blood*. 2016;128(suppl 22).[6]

Safety and Activity of Brentuximab Vedotin (BV) Plus Ifosfamide, Carboplatin, and Etoposide (ICE) for Relapsed/Refractory (Rel/Ref) Classical Hodgkin Lymphoma (cHL): Initial Results of a Phase I/II Trial

A phase 1/2 study investigated the addition of brentuximab vedotin to ifosfamide, carboplatin, and etoposide (ICE) in patients with classical HL who had relapsed after first-line treatment or had primary refractory disease (Abstract 1834). Patients were excluded from the study if they had received prior treatment with brentuximab vedotin or recent treatment with chemotherapy. A 3 + 3 dose-escalation design was used to determine the maximum tolerated dose of brentuximab vedotin in combination with ICE. Among the 16 patients who completed study treatment, 44% had advanced-stage disease at diagnosis, all had received first-line ABVD, 69% had achieved a CR with initial treatment, and 31% had received prior radiotherapy. One AE consisting of grade 4 sepsis was classified as a dose-limiting toxicity. The maximum tolerated dose was established as brentuximab vedotin at 1.5 mg/kg on days 1 and 8 plus ICE in two 21-day cycles. The ORR was 94%, including 88% CRs. After a median follow-up of 10.5 months, all patients were alive. All stem cell collection procedures were successful.

score of 1 or 2, and 3 had a Deauville score of 3. (The score was not reported for 1 patient.) Peripheral blood immunophenotyping was performed to determine the effect of treatment on various cell types. At baseline, a high percentage of regulatory T cells were shown to express CD30. After administration of single-agent brentuximab vedotin during cycle 1, no effect was observed on CD4-positive cells, but there was evidence of a decrease in immunosuppressive regulatory T cells. After administration of nivolumab on day 8 of cycle 1, the proportion of activated and dividing CD4-positive cells increased.

Nine patients were able to proceed to autologous SCT. There was no evidence that treatment with the combination of brentuximab vedotin plus nivolumab had any impact on stem cell mobilization or engraftment. The median number of apheresis sessions was 2 (range, 1-3), the median total number of CD34-positive cells harvested was 7.9 cells/kg (range, 4-26), the median time to neutrophil engraftment was 11.5 days (range, 9-15), and the median time to platelet engraftment was 16 days (range, 12-20).

Five percent of patients had discontinued before completing study treatment, 21% had initiated autologous SCT, and 5% had received an alternative salvage therapy prior to autologous SCT. Patients had received a median of 4 doses of the 2 antibodies (range, 1-4 doses). No patients discontinued treatment owing to an AE. Infusion-related reactions leading to dose interruption occurred in 26% of patients receiving brentuximab vedotin and 7% of those receiving nivolumab.

The most common treatment-emergent AEs of any grade were fatigue, nausea, infusion-related reactions, and pruritus, each occurring in approximately 30% to 40% of patients. All AEs observed in 10% or more of patients were grade 1 or 2, with the exception of 1 patient who experienced grade 3 urticaria. Infusion-related reactions were observed in 38% of patients, including 1 patient with a grade 3 reaction. The most common symptoms included flushing (14%), nausea (14%), chest discomfort (12%), dyspnea (12%), urticaria (12%), cough (10%), and pruritus (10%). The study protocol was amended to require premedication with low-dose corticosteroids and antihistamines at cycles 2 to 4, but the rate and severity of infusion-related reactions did not change. Potential immune-related AEs of any grade included infusion-related reaction (36%), rash (29%), diarrhea (26%), transaminase elevation (10%), and hypothyroidism (5%). All of these events were grade 1 or 2, with the exception of 1 patient (2%) who experienced a grade 3/4 transaminase

elevation. There were no reports of pneumonitis or colitis. Four patients received topical corticosteroids for rash and infusion-related reactions. Five patients received systemic corticosteroids for infusion-related reactions, and 1 patient each received systemic corticosteroids for urticaria, rash, pruritus, ear itching, or elevated alanine transaminase.

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BEACOPP Escalated Followed by Radiotherapy of Initial Bulk or Residual Disease in Advanced Stage Hodgkin Lymphoma: Long-Term Follow Up of the HD9 and HD12 Trials of the German Hodgkin Study Group

In trial HD9 from the German Hodgkin Study Group (GHSG), patients were randomly assigned to 1 of 3 chemotherapy regimens: 4 cycles of cyclophosphamide, vincristine, procarbazine, and prednisone alternating with ABVD (COPP-ABVD); 8 cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (standard BEACOPP); or 8 cycles of escalated BEACOPP, which contains increased doses of etoposide, doxorubicin, and cyclophosphamide.[1] When indicated, treatment was followed by local radiotherapy. Enrollment in the COPP-ABVD group was stopped in 1996 based on inferior results. The trial established 8 cycles of escalated BEACOPP followed by radiotherapy at sites of initial bulky disease or residual tumors as the standard of care for patients with advanced HL.

Subsequently, trial HD12 evaluated a reduced-intensity regimen in an effort to improve tolerability while maintaining efficacy.[2] HD12 compared 8 cycles of escalated BEACOPP vs 4 cycles of escalated BEACOPP followed by 4 cycles of standard BEACOPP with concomitant radiotherapy (the 4 + 4 regimen), but with no radiotherapy at sites of initial bulk or residual disease. The trial enrolled 1670 patients between January 1999 and January 2003. After 5 years of follow-up, the reduced-intensity regimen did not substantially reduce rates of severe toxicity and may have yielded decreased efficacy compared with escalated BEACOPP.

Dr Bastian von Tresckow of the University of Cologne in Cologne, Germany presented long-term follow-up from the GHSG HD9 and HD12 trials.[3] After a median observation time of 141 months, the 15-year estimate of cumulative secondary malignancies was similar for patients treated with 4 cycles of COPP/ABVD (7.2%), 8 cycles of standard BEACOPP (9.1%), or 8 cycles of escalated BEACOPP (11.4%). The estimated 15-year PFS confirmed the initial finding that showed superior efficacy with escalated BEACOPP. Fifteen-year PFS estimates were 57.0% for patients treated with 4 cycles of COPP/ABVD, 66.8% for patients treated with 8 cycles of standard BEACOPP (HR vs 4 cycles of COPP/ABVD, 0.73), and 74.0% for patients treated with 8 cycles of escalated BEACOPP (HR vs 4 cycles of COPP/ABVD, 0.53). The difference in estimated 15-year PFS for 4 cycles of COPP/ABVD vs 8 cycles of escalated BEACOPP was 17.0%. The intensified regimen also yielded an improved OS. The estimated 15-year OS was 72.3% with 4 cycles of COPP/ABVD, 74.5% with 8 cycles

of standard BEACOPP, and 80.9% with 8 cycles of escalated BEACOPP.

In HD12, patients with sites of initial bulk or residual disease were randomly assigned to receive radiotherapy or no further treatment. After a median observation time of 95 months to 100 months, the rates of secondary malignancies in the HD12 patients receiving 8 cycles of escalated BEACOPP were 9.2% with radiotherapy vs 6.3% without radiotherapy. These rates were 5.9% vs 6.1% for patients receiving the 4 + 4 regimen with or without radiotherapy, respectively. The standardized incident ratios ranged from 2.3 to 3.2 for the 4 treatment arms, with overlapping confidence intervals. Comparison of the 2 chemotherapy regimens yielded similar survival outcomes. After a median observation time of 105 months, the median estimated 10-year OS for treatment was 87.3% with 8 cycles of escalated BEACOPP vs 86.8% with the 4 + 4 regimen, with no difference in risk (HR, 1.0; 95% CI, 0.7-1.4).

In contrast, radiotherapy was associated with an improved PFS. After a median observation time of 97 months, median estimated 10-year PFS was 86.8% for patients who received radiotherapy vs 82.2% for patients who did not. The results were confounded by the fact that 229 patients in the radiotherapy group did not receive radiotherapy, and 69 patients in the no-radiotherapy group did receive radiotherapy. With a median observation time of 100 months, analysis of the patients based on actual radiotherapy exposure yielded median estimated 10-year PFS rates of 89.8% in patients without radiotherapy exposure vs 83.3% in patients with radiotherapy to initial bulk or residual tumors. Similarly, OS analysis based on actual treatment revealed a superior outcome with radiotherapy. With a median observation time of 107 months, the median estimated 10-year OS was 93.7% in patients treated with radiotherapy and 90.4% in patients without radiotherapy. In patients with residual lesions only, the difference in OS was even more pronounced. After a median observation time of 108 months, median estimated 10-year OS was 94.4% in patients who received radiotherapy vs 88.4% in patients who did not.

The long-term analysis confirmed earlier results observed in patients with advanced HL. Despite a potential increase in the rate of secondary cancers, escalated BEACOPP was superior to 4 cycles of COPP/ABVD in terms of PFS and OS. Eight cycles of escalated BEACOPP plus radiotherapy in patients with initial bulk or residual disease was associated with a 15-year PFS of 74% and a 15-year OS of 80.9%. Radiotherapy was particularly beneficial in patients with residual lesions after chemotherapy. The current GHSG strategy for this patient population is 6 cycles of escalated BEACOPP followed by radiotherapy of residual lesions based on imaging with positron emission tomography.

ABSTRACT SUMMARY Pembrolizumab for Treatment of Relapsed/Refractory Mycosis Fungoides and Sézary Syndrome: Clinical Efficacy in a CITN Multicenter Phase 2 Study

A phase 2 trial from the Cancer Immunotherapy Trials Network evaluated pembrolizumab in 24 patients with relapsed/refractory mycosis fungoides or Sézary syndrome (Abstract 181). The ORR was 38%, consisting of 1 CR and 8 PRs. Among the patients who responded, 6 had 90% or greater improvement in skin disease. Stable disease was reported in an additional 38% of patients. The median time to response was 11 weeks (range, 8-41 weeks). Responses were durable, with 8 of 9 continuing at the time the study was reported. Responses were seen regardless of the patients' disease stage, disease type, and number of prior systemic therapies. At the time of the analysis, the median PFS had not yet been reached, and the 1-year PFS was 69%. Skin tissue expression of PD-1, PD-L1, PD-L2, or infiltrating CD8-positive T cells did not impact treatment response.

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A Phase I Study With an Expansion Cohort of the Combination of Ipilimumab and Nivolumab and Brentuximab Vedotin in Patients With Relapsed/Refractory Hodgkin Lymphoma: A Trial of the ECOG-ACRIN Cancer Research Group (E4412 Arms D and E)

The phase 1 E4412 trial was designed to test the hypothesis that targeting tumor cells with brentuximab vedotin and concomitantly activating immune cells in the tumor microenvironment would improve outcomes in HL patients.[1] Eligible patients were adults with relapsed or refractory HL and measurable disease. Exclusion criteria included use of brentuximab vedotin during the prior 6 months, relapse within 6 months of receiving prior brentuximab vedotin, and prior nivolumab treatment. Three patients were initially enrolled in arm D (dose level 1), in which they received nivolumab at 3 mg/kg on day 1 of cycles 1 to 46 plus brentuximab vedotin at 1.2 mg/kg on day 1 of cycles 1 to 16, in 3-week cycles. Seven patients in arm E (dose level 2) received nivolumab as in arm D plus a higher dose of brentuximab vedotin, 1.8 mg/kg, given on day 1 of cycles 1 to 16. Arm F was the phase 1 expansion cohort, and 9 patients in this arm received the same treatment as patients in arm E. Brentuximab vedotin and nivolumab were administered on the same day, with brentuximab vedotin administered first, followed by 1 hour of observation, and subsequent administration of nivolumab. Responses were assessed by the investigator. A Deauville score of 1 or 2 was required for CR. Imaging was performed at study start and at 12 weeks, then every 3 months.

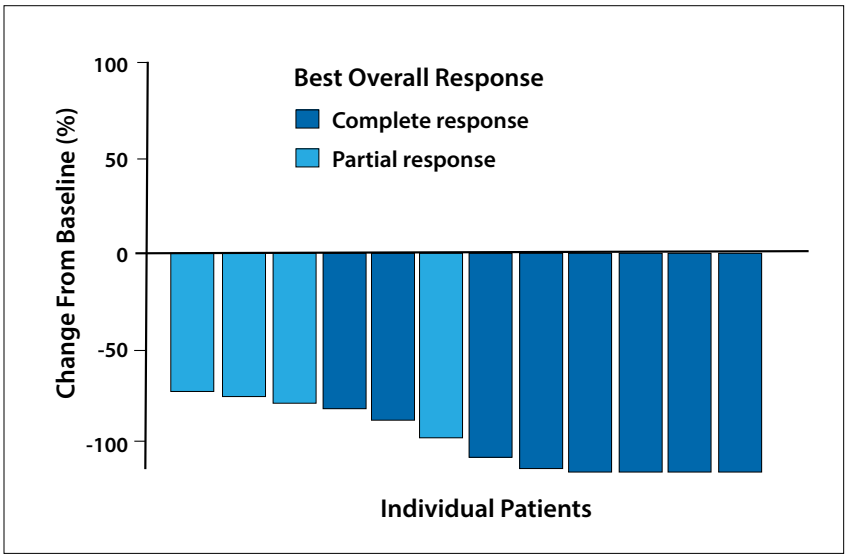

Figure 5. Overall response in a phase 1 study of nivolumab and brentuximab vedotin in patients with relapsed/refractory Hodgkin lymphoma. Adapted from Diefenbach CS et al. ASH abstract 1106. *Blood*. 2016;128(suppl 22).[1]

The primary objective of the study was to determine the maximum tolerated dose and dose-limiting toxicities of the regimen. Secondary objectives included response rates, clinical benefit, response duration, and survival. Correlative studies included tumor-specific T-cell immunity, systemic cytokine and T-cell specific profiles, and gene expression profiling to determine a response vs resistance signature.

The 19 enrolled patients had a median age of 40 years (range, 21-70 years), and 53% were male. Patients had a baseline ECOG PS of 0 (57%), 1 (32%), or 2 (11%). Twenty-six percent of patients had B symptoms, and the median number of prior systemic therapies was 3 (range, 1-7). Forty-two percent of patients had received prior SCT, and 21% had received prior treatment with brentuximab vedotin. One patient required a brentuximab vedotin dose reduction. In 2 patients, the dose of brentuximab vedotin was delayed. Nivolumab dose delays occurred in 2 patients.

In the population of 12 evaluable patients, the ORR was 100%, including 66% CRs (Figure 5). Two patients had received prior brentuximab vedotin, and both of these patients achieved a CR. After a median follow-up of 4.7 months, median PFS was 8.5 months (Figure 6). After a median follow-up of 3.5 months, median OS was not reached. The durability of responses will be evaluated when longer follow-up data are available, and correlative studies are continuing.

Treatment was generally well-

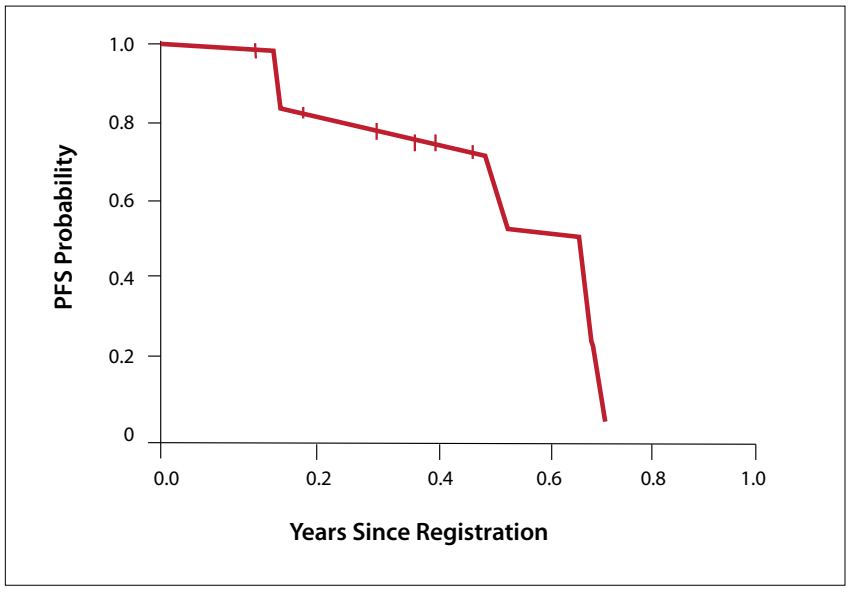

Figure 6. Median PFS in a phase 1 study of nivolumab and brentuximab vedotin in patients with relapsed/refractory Hodgkin lymphoma. PFS, progression-free survival. Adapted from Diefenbach CS et al. ASH abstract 1106. *Blood*. 2016;128(suppl 22).[1]

tolerated. The most common AE of any grade was elevation of hepatic enzymes, which occurred primarily in cycle 1, consisted of grade 1/2 events, and was transient, with no impact on treatment. The second most common AE of any grade was grade 1/2 peripheral sensory neuropathy, observed most frequently in patients who had received prior brentuximab vedotin. Other common AEs of any grade included nausea, maculopapular rash, headache, and fever. Six grade 3 to 5 AEs were observed.

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Five-Year Survival Data From a Pivotal Phase 2 Study of Brentuximab Vedotin in Patients With Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma

An open-label, multicenter, pivotal phase 2 study evaluated the safety and efficacy of brentuximab vedotin in patients with relapsed or refractory systemic ALCL.[1] Eligible patients had CD30-positive relapsed or refractory systemic ALCL, were at least 12 years old, had measurable disease, and had an ECOG PS of 0 or 1. The first patient was enrolled in June 2009, and all patients had completed treatment by June 2011. Patients received brentuximab vedotin (1.8 mg/kg) on day 1 of 21-day cycles for up to 16 cycles. The primary endpoint was ORR based on independent review, with a secondary endpoint of OS. Additional prespecified endpoints included PFS and ORR according to investigator review.

The study enrolled 58 patients with a median age of 52 years (range, 14-76 years). Fifty-seven percent of patients were male, and all but 1 patient had an ECOG PS of 0 or 1. Seventy-two percent of patients had anaplastic lymphoma kinase (ALK)-negative disease, 62% had disease that was refractory to first-line therapy, and 26% had previously undergone autologous SCT.

The initial ORR based on independent review was 86%, including 59% CRs.[2] The most common AEs of grade 3 or higher were neutropenia (21%), peripheral neuropathy (17%), and thrombocytopenia (14%). Peripheral neuropathy occurred in 57% of patients; the majority of cases were grade 1 or 2. The peripheral neuropathy completely resolved in 67% of patients, and no grade 3 cases were evident at last follow-up. In 8 of 11 patients with ongoing peripheral neuropathy at last follow-up, the maximum severity was grade 1. In patients whose peripheral neuropathy resolved, the median time from onset to resolution was 14 weeks.

Five-year follow-up data were presented by Dr Barbara Pro.[3] After a median observation time of 71.4 months, the estimated 5-year OS was 60% (Figure 7), the median OS

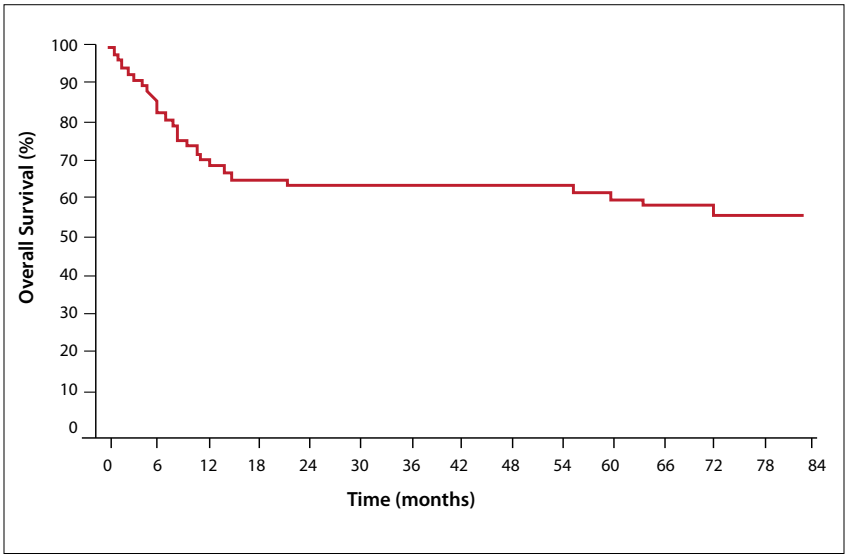

Figure 7. Estimated 5-year overall survival in a phase 2 study of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma. Adapted from Pro B et al. ASH abstract 4144. *Blood*. 2016;128(suppl 22).[3]

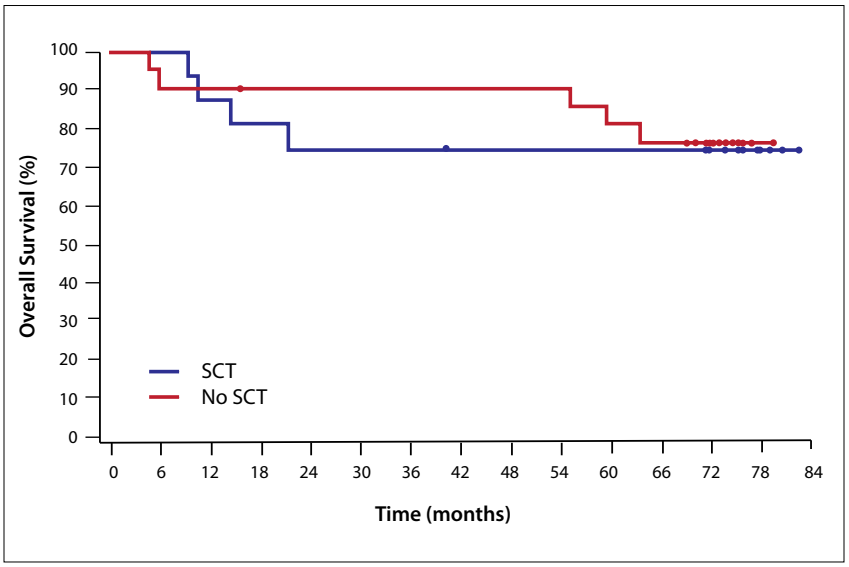

Figure 8. In a phase 2 study of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma, the median overall survival was not reached among patients with a complete response who did not undergo consolidative SCT. SCT, stem cell transplant. Adapted from Pro B et al. ASH abstract 4144. *Blood.* 2016;128(suppl 22).[3]

was not estimable, and the median PFS was 20.0 months. The estimated 5-year OS rate was 61% in patients with ALK-negative disease vs 56% in those with ALK-positive disease. In the 38 patients who achieved a CR with brentuximab vedotin, response duration ranged from 0.9 months to 79.7+ months. The median response duration was not reached. Among the patients who achieved a CR, 16 subsequently underwent consolidative allogeneic or autologous SCT. Median OS and median PFS were not reached in these patients. In the 22 patients with CR who did not undergo consolidative SCT, the median OS was not reached (Figure 8), and the median PFS was 39.4 months. The ongoing phase 3 ECHELON-2 trial (A Comparison of Brentuximab Vedotin and CHP With Standard-of-Care CHOP in the Treatment of Patients With CD30-Positive Mature T-Cell Lymphomas) is evaluating brentuximab vedotin in combination with cyclophosphamide, doxorubicin, and prednisone vs CHOP as first-line treatment for CD30-expressing peripheral T-cell lymphomas, including systemic ALCL.[4]

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CheckMate 205 Update With Minimum 12-Month Follow Up: A Phase 2 Study of Nivolumab in Patients With Relapsed/Refractory Classical Hodgkin Lymphoma

In patients with relapsed or refractory classical HL following autologous SCT, historical PFS data suggest that the durability of response to subsequent brentuximab vedotin corresponds with the depth of response. In a phase 2 study, 102 HL patients who had relapsed following autologous SCT were treated with brentuximab vedotin (1.8 mg/kg) every 3 weeks for a maximum of 16 cycles.[1] The ORR was 75%, including 34% CRs. The median PFS for the entire study group was 5.6 months. Median response duration was 20.5 months for patients who achieved a CR and 6.7 months for patients who achieved a PR. Classical HL is characterized by malignant cells with alterations at the 9p24.1 locus that result in overexpression of the PD-1 ligands, PD-L1 and PD-L2, suggesting that silencing of the immune checkpoint pathway could enhance killing of malignant HL cells.[2] Nivolumab targets PD-1 and is approved by the US Food and Drug Administration for treatment of classical HL that has relapsed or progressed after autologous SCT and posttransplant treatment with brentuximab vedotin. The Checkmate 205 (Study of Nivolumab in Patients With Classical Hodgkin's Lymphoma) trial investigated the efficacy and safety of single-agent nivolumab (3 mg/kg) every 2 weeks in patients with classical HL after failure of autologous SCT.[3] Cohort A included 63 patients who had no exposure to brentuximab vedotin after SCT and cohort B included 80 patients who received brentuximab vedotin after SCT. Patients in cohort A vs cohort B had a median age of 33 years (range, 18-65 years) vs 37 years (range, 18-72 years), respectively. All patients had an ECOG PS of 0 or 1. The median number of previous therapies was 2 (range, 2-8) in cohort A and 4 (range, 3-15) in cohort B. In cohort A, 32% of patients had received systemic cancer therapy or radiotherapy following autologous SCT. The primary endpoint was the ORR following a prespecified minimum follow-up period of 6 months, as assessed by independent review. Among 80 patients in cohort B, the primary endpoint analysis showed an ORR of 66%. The median PFS was 10 months, and the response duration was 8 months.

Dr John Timmerman presented initial findings from cohort A and updated findings from cohort B.[4] Minimum follow-up was 9 months in cohort A vs 12 months in cohort B. In cohort A, 93% of 63 evaluable patients showed a reduction in tumor burden. The ORR was 68%, including 14 patients with a CR (Table 1). Responses generally occurred fairly

Table 1. Best Overall Response in a Phase 2 Trial of Nivolumab in Relapsed/Refractory Classical Hodgkin Lymphoma

Response	n (%)
Overall response rate	43 (68)
Complete response	14 (22)
Partial response	29 (46)
Stable disease	13 (21)
Partial disease	7 (11)

Adapted from Timmerman JM et al. ASH abstract 1110. *Blood*. 2016;128(suppl 22).[4]

Brentuximab Vedotin Plus ESHAP (BRESHAP) Is a Highly Effective Combination for Inducing Remission in Refractory and Relapsed Hodgkin Lymphoma Patients Prior to Autologous Stem Cell Transplant: A Trial of the Spanish Group of Lymphoma and Bone Marrow Transplantation (GELTAMO)

A study from the Spanish Group of Lymphoma and Bone Marrow Transplantation (GELTAMO) evaluated brentuximab vedotin plus etoposide (40 mg/m^2) on days 1 to 4, methylprednisolone (250 mg) on days 1 to 4, high-dose cytarabine (2 g/m^2) on day 5, and cisplatin (25 mg/m^2) on days 1 to 4 (BRESHAP) in patients with relapsed or refractory HL. The phase 1 portion established 1.8 mg/m^2 on day 1 as the appropriate dose of brentuximab vedotin (Garcia-Sanz R et al. 2015 ASH Abstract 582). Results for the phase 2 portion were presented at the 2016 ASH meeting (Abstract 1109). Among 66 patients, 61% had primary refractory disease, 41% had extranodal disease, 18% had received prior radiotherapy, and 30% had B symptoms. Following treatment, the ORR was 95%, including 71% CRs. The most common nonhematologic AEs of any grade were fever (27%), mucositis (27%), and pain (25%). Twenty-three serious AEs were reported, including fever (n=13), hypomagnesemia (n=3), and viral infection (n=2). One patient died from nonneutropenic abdominal sepsis, and 1 patient died from pulmonary embolism. There were no collection failures among the 64 patients who proceeded to stem cell transplant.

ABSTRACT SUMMARY Pembrolizumab in Relapsed/Refractory Classical Hodgkin Lymphoma: Primary End Point Analysis of the Phase 2 KEYNOTE-087 Study

The phase 2 KEYNOTE-087 study investigated the efficacy and safety of pembrolizumab, a PD-1 inhibitor, in patients with relapsed or refractory classical HL (Abstract 1107). The study enrolled 3 subtypes of patients: those who developed relapsed or refractory disease after autologous SCT and treatment with subsequent brentuximab vedotin (cohort 1); those who were ineligible for autologous SCT owing to chemoresistance and brentuximab vedotin therapy failure (cohort 2); and those with relapsed or refractory disease after autologous SCT who did not receive treatment with subsequent brentuximab vedotin (cohort 3). Based on blinded independent central review, the ORR for the entire study group of 210 patients was 69.0% (95% CI, 62.3%–75.2%), including 22.4% CRs. The ORR was 73.9% (95% CI, 61.9%–83.7%) in cohort 1, 64.2% (95% CI, 52.8%–74.6%) in cohort 2, and 70.0% (95% CI, 56.8%–81.2%) in cohort 3. The rate of CR in the 3 cohorts was 21.7%, 24.7%, and 20.0%, respectively. In patients with primary refractory vs relapsed disease, the ORR was 79.5% vs 67.8%, respectively. The fixed dose of pembrolizumab (200 mg) every 3 weeks was associated with an acceptable toxicity profile.

quickly in the brentuximab vedotin–naive patients, with a median time to response of 2 months (range, 2-6 months). After a median follow-up of 14 months (range, 1-20 months), the median duration of response and the median PFS were not reached overall, nor in the subsets of patients who had achieved a CR or PR. Nine-month PFS was 68%, and 9-month OS was 97%.

Six patients in cohort A and 11 patients in cohort B proceeded to allogeneic hematopoietic SCT after nivolumab treatment. The median time from last nivolumab dose to transplant was 158 days (range, 27-411 days) in cohort A vs 38 days (range, 23-271 days) in cohort B. In cohort B, 4 patients experienced grade 2 to 4 graft-vs-host disease. There were no deaths from disease progression reported among patients who proceeded to allogeneic hematopoietic SCT, and no transplant-related mortality occurred. In cohort B, the median follow-up was 15 months (range, 2-19 months). The ORR was 68%, including 6 patients (7.5%) with a CR, and 95% of patients showed a reduction in tumor burden. The median duration of response was 13 months. Among patients who achieved a CR, the median duration of response was not reached. It was 13 months among patients who achieved a PR. Twelve-month OS was 95%.

At the time of this analysis, most patients remained on treatment (62% in cohort A vs 54% in cohort B). Reasons for discontinuing treatment included disease progression (25% in cohort A vs 24% in cohort B), nivolumab toxicity (3% vs 6%), and AEs unrelated to study drug (2% vs 1%). Toxicities leading to study drug discontinuation included hepatic-related events (n=4), pneumonitis (n=2), and syncope (n=1). In cohort A, the most common drug-related AEs of any grade included fatigue (29%), diarrhea (21%), rash (13%), and pruritus (13%). In cohort B, the most common drug-related AEs of any grade were fatigue (29%), infusion-related reaction (20%), rash (15%), and arthralgia (15%). Drug-related grade 3/4 AEs occurred in 11% of patients in cohort A and 30% in cohort B. Drug-related serious AEs were reported in 1 patient in each cohort. No treatment-related deaths occurred in either cohort.

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Highlights in Lymphoma From the 2016 American Society of Hematology Annual Meeting and Exposition: Commentary

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Several abstracts presented at the 2016 American Society of Hematology (ASH) meeting provided data that may impact the management of patients with lymphoma. New and updated study data were presented for T-cell lymphoma, B-cell lymphoma, and classical Hodgkin lymphoma.

T-Cell Lymphoma

Two studies of newer therapeutic approaches in T-cell lymphoma, both in cutaneous T-cell lymphoma, were practice-changing or at least practice-informing.

Brentuximab Vedotin

The ALCANZA trial (A Phase 3 Trial of Brentuximab Vedotin [SGN-35] Versus Physician's Choice [Methotrexate or Bexarotene] in Patients With CD30-Positive Cutaneous T-Cell Lymphoma) was one of the more impactful studies presented at the 2016 ASH meeting. Dr Youn Kim presented results from this phase 3, international study, which enrolled 131 patients with mycosis fungoides or anaplastic large cell lymphoma.[1] ALCANZA is a randomized study, which is rare in this setting. The investigational arm was brentuximab vedotin, and the control arm was an investigator's choice of either methotrexate or bexarotene. One audience question about this study concerned the selection of the therapies for the control arm. The choice was based primarily on the availability of standard agents at all of the participating centers, which included sites in Europe and Australia. Methotrexate and bexarotene are among the more commonly available and commonly used systemic therapies for cutaneous T-cell lymphoma worldwide.[1] Several of the agents available in the United States, such as romidepsin and pralatrexate, are not available in some countries.

All patients with mycosis fungoides had received previous systemic treatment, and had a CD30 expression of at least 10% on tumor cells or the lymphoid infiltrate as assessed by central pathology review of at least 2 skin biopsies. Patients with anaplastic large cell lymphoma, which is always CD30-positive, had relapsed after prior systemic therapy or radiation therapy.

The ALCANZA trial used a novel primary endpoint known as overall response rate 4 (ORR4), which was defined as a global response (encompassing response in skin, lymph nodes, and blood) that lasted at least 4 months. In many studies of cutaneous T-cell lymphoma, because the disease is visible and very symptomatic, there is a tendency for patients with minimal response or stable disease to discontinue treatment and switch therapy before they develop defined progressive disease. Consequently, those patients

ABSTRACT SUMMARY A LYSA Phase II Study of Oral JAK1/2 Inhibitor Ruxolitinib in Advanced Relapsed/Refractory (R/R) Hodgkin Lymphoma (HL)

Ruxolitinib, an oral inhibitor of JAK 1/2, was evaluated in a phase 2 study of patients with advanced relapsed or refractory HL (Abstract 4160). Ruxolitinib (20 mg) was administered twice daily for six 28-day cycles, with maintenance therapy allowed for patients exhibiting disease control. The 33 enrolled patients had received a median 5 prior lines of therapy (range, 1-16). Sixty-nine percent of patients had stage III/IV disease, and 82% were refractory to their most recent prior therapy. After induction, the ORR was 9.4%, with no CRs. The best ORR at any time during the study was 18.8%, and included 1 patient (3%) with a CR. The median duration of response was 7.7 months (95% CI, 1.8 months-not reached). Ruxolitinib did not meet the threshold level for activity based on the primary endpoint of response at 6 months. There were 40 AEs of any grade observed in 14 patients. Eighteen were of grade 3 or greater, and 8 AEs were serious. No AEs led to death.

who switch therapy without progression may be censored from assessment of progression-free survival (PFS), and/or their PFS may be impacted by subsequent therapy. To compensate for this occurrence, ORR4 was designed in consultation with the US Food and Drug Administration (FDA) and key experts to identify responses of sufficient degree and duration as to be clinically meaningful. Secondary endpoints included complete response rate and PFS.

The results showed that brentuximab vedotin was significantly better than the standard arm of methotrexate or bexarotene.[1] The ORR4 was 56% for brentuximab vedotin vs 12.5% for the physician's choice of treatment. The complete response rate was 15.6% for brentuximab vedotin and just 1.6% for physician's choice. The median PFS was more than 16 months for brentuximab vedotin vs less than 4 months for physician's choice. Quality-of-life assessments also showed significant benefit for brentuximab vedotin.

Historically, many systemic therapies for cutaneous T-cell lymphoma were associated with moderate response rates in phase 2 trials. It was difficult to know whether one agent was more active than another, and selection was based on factors such as toxicity, ease of administration, and cost. With ALCANZA, however, there is now a randomized study that clearly shows significantly better activity for one drug, brentuximab vedotin, over some standard therapies. These results will surely factor into the selection and sequencing of therapy for patients with cutaneous T-cell lymphoma.

One caveat to this new approach concerns cumulative toxicity. A common principle of management for this disease was to select milder therapies and give them until progression or intolerance. Many of the standard drugs used in this setting, such as bexarotene, methotrexate, vorinostat, and romidepsin, are not associated with cumulative toxicity.[2] Brentuximab vedotin has neuropathy as a cumulative toxicity. It cannot be given indefinitely. In the ALCANZA trial, the average number of cycles was 12. Physicians will need to balance the benefits of the higher response rate, which correlated with quality-of-life improvement, against the cumulative toxicity of neuropathy, which often leads to treatment discontinuation.

ABSTRACT SUMMARY Pembrolizumab in Patients With Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure: Long-Term Efficacy From the Phase 1b KEYNOTE-013 Study

The phase 1b KEYNOTE-013 study evaluated pembrolizumab (10 mg/kg) every 2 weeks in a cohort of patients with relapsed or refractory classical HL (Abstract 1108). Patients were required to have failed prior brentuximab vedotin and to have failed or be ineligible for treatment with autologous SCT. Of the 31 patients, 29% had bulky disease, 32% had B symptoms, and 74% had failed prior autologous SCT. The median number of prior lines of therapy was 5 (range, 2-15). After a median follow-up of 29 months, the most common treatment-related AEs of any grade were diarrhea (occurring in 19%), and hypothyroidism, pneumonitis, and nausea (each observed in 13% of patients). Treatment-related grade 3/4 AEs were observed in 19% of patients. Based on blinded independent central review, the ORR was 58%, with 19% CRs. In the 13 patients with primary refractory disease, the ORR was 62%, and the CR rate was 31%. In the 18 patients without primary refractory disease, the ORR was 56%, with 11% CRs.

Pembrolizumab

A multicenter, phase 2 trial of pembrolizumab from the Cancer Immunotherapy Trials Network provided data on another new option for relapsed mycosis fungoides and Sézary syndrome. Dr Michael Khodadoust presented preliminary results.[3] Treatments for mycosis fungoides and Sézary syndrome are associated with responses that have some durability, but they do not cure the disease. There is almost always a need for subsequent lines of therapy. In many of these patients, particularly those with Sézary syndrome, tumor cells express programmed death 1 (PD-1).[4] Pembrolizumab inhibits PD-1. Data on checkpoint inhibitors in cutaneous T-cell lymphomas are limited. The minimal data available for these patients from the nivolumab studies showed mostly stable disease and few responses.[5]

The study enrolled 15 patients with Sézary syndrome and 9 with mycosis fungoides. Patients with mycosis fungoides had stage 1b or higher disease, and all had relapsed after prior systemic therapy.

The overall response rate was 38%.[3] Responses were seen across all subgroups, including patients with Sézary syndrome and advanced-stage disease. Some of the responses were fairly durable. Although the follow-up was relatively short, there were ongoing responses beyond 6 months and beyond a year. Most of the responses occurred within the first 2 months of treatment.

Some patients developed red, inflamed skin that resembled progression of disease. However, biopsies showed this reaction to be a flare from the treatment, and some of these patients subsequently responded. The study is also analyzing immune correlates to identify predictors of response, but results are not yet available.

Pembrolizumab is currently FDA-approved for other settings, such as advanced melanoma, non–small cell lung cancer, and head and neck squamous cell cancer. This study will

likely stimulate additional studies of checkpoint inhibition in cutaneous T-cell lymphoma and other T-cell lymphomas.

B-Cell Lymphoma

There were several abstracts in B-cell lymphoma. Two have the potential to change clinical practice.

Obinutuzumab

The international, randomized, phase 3 GALLIUM study (A Study of Obinutuzumab [RO5072759] Plus Chemotherapy in Comparison With MabThera/Rituxan [Rituximab] Plus Chemotherapy Followed by GA101 or MabThera/Rituxan Maintenance in Patients With Untreated Advanced Indolent Non-Hodgkin's Lymphoma) evaluated obinutuzumab in patients with previously untreated, indolent non-Hodgkin lymphoma. In the ASH plenary session, Dr Robert Marcus presented results for the follicular lymphoma cohort (n=1201).[6] These patients had grade 1 to 3a disease that was advanced stage or bulky. Most of the patients had advanced-stage disease and high scores on the Follicular Lymphoma International Prognostic Index (FLIPI). Approximately half of the patients had bulky disease. These patients therefore had a high tumor burden and were an appropriate population to receive chemoimmunotherapy.

Patients were randomly assigned to receive induction therapy with obinutuzumab plus chemotherapy or rituximab plus chemotherapy. The chemotherapy regimen could consist of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); cyclophosphamide, vincristine, and prednisone (CVP); or bendamustine. Each institution involved in the study was permitted to preselect a chemotherapy regimen that was used by all of its enrolled patients. When interpreting the results, it is important to know that there was no individual bias impacting which patients received which regimen.

Patients who achieved a complete or partial response then went on to receive maintenance therapy. Those in the obinutuzumab induction arm received obinutuzumab maintenance, and those in the rituximab induction arm received rituximab maintenance.

At the end of induction therapy, the overall response was similar in both treatment arms, at 86.9% for patients receiving rituximab plus chemotherapy and 88.5% for patients receiving obinutuzumab plus chemotherapy.[6] Differences, however, appeared after maintenance therapy. PFS was significantly improved with obinutuzumab and chemotherapy. The 3-year PFS was 80% for obinutuzumab plus chemotherapy vs 73% for rituximab plus chemotherapy (hazard ratio, 0.66). A similar benefit with obinutuzumab was seen in time to next therapy, another endpoint. At 3 years, 87.1% of the obinutuzumab group did not require therapy vs 81.2% of the rituximab group (hazard ratio, 0.68). There was no difference in terms of overall survival, at a median follow-up of just under 3 years. In this study, obinutuzumab plus chemotherapy appeared to provide similar response and better durability than rituximab plus chemotherapy.

There was a mild imbalance in terms of toxicity, with numerically higher instances of febrile neutropenia and infection in the obinutuzumab plus chemotherapy arm. Not surprisingly, infusion-related events were significantly higher in the obinutuzumab arm.

Another interesting and unexpected finding from this study that may impact practice was an increased number of fatal adverse events among patients treated with bendamustine. There were more grade 5 adverse events in the bendamustine-containing regimens, as compared with CHOP or CVP, regardless of whether patients also received obinutuzumab or rituximab. These deaths spanned a number of different etiologies, including pneumonia, respiratory and other infections, sepsis, and bacteremia. Some clinicians believe that this difference is an accurate reflection of increased toxicity and risk with bendamustine, whereas others view it as more of an isolated finding in this study alone.

The takeaways from this study are that obinutuzumab in combination with chemotherapy, when compared with rituximab in combination with chemotherapy, had superior activity in terms of PFS at the cost of some modest increase in toxicity, and that bendamustine as part of chemoimmunotherapy resulted in a higher number of toxicity-related deaths than CHOP or CVP. These findings have led some clinicians to reconsider using bendamustine as a standard chemotherapy for patients with follicular lymphoma. Use of bendamustine is particularly being questioned in younger patients who are likely to tolerate CHOP reasonably well.

R-CHOP vs Dose-Adjusted EPOCH-R

An important, and long-awaited, phase 3 trial from the US Intergroup, led by the Alliance for Clinical Trials in Oncology, randomly assigned patients with untreated diffuse large B-cell lymphoma to receive rituximab plus CHOP (R-CHOP) or rituximab plus dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH-R).[7] This long-term study was based on preliminary data, largely from the National Cancer Institute, suggesting that dose-adjusted EPOCH-R may provide higher activity in these patients overall or in certain subsets. The study enrolled more than 500 patients.

There were no significant differences between the 2 treatments.[7] Overall response rates were approximately 89% in each arm. Complete response rates were 62% for R-CHOP and 61% for dose-adjusted EPOCH-R. There

were no significant differences in event-free survival and overall survival.

There was some increased toxicity, primarily hematologic events, in the dose-adjusted EPOCH-R arm. These patients experienced more high-grade thrombocytopenia, neutropenia, and febrile neutropenia. EPOCH is dose-adjusted based on the nadir counts, so it is expected that if the dose is escalated based on lack of a sufficient nadir, it will push more patients toward higher grades of hematologic toxicity. There was also more neuropathy in the dose-adjusted EPOCH-R arm.

In subset analyses, the study stratified patients according to International Prognostic Index scores, to see whether outcome varied according to low, intermediate, or high risk. The numbers are too small to draw any firm conclusions, but there was at least a possibility that higher-risk patients may have achieved benefit from dose-adjusted EPOCH-R. Confirmation of this observation will of course require further study. The study authors are performing subset analysis based on cell of origin to determine whether EPOCH-R might be better for certain subtypes of large B-cell lymphoma. Those data were not yet available.

Hodgkin Lymphoma

There were updates on the use of checkpoint inhibitors in patients with Hodgkin lymphoma. Long-term analysis of the phase 2, single-agent studies of pembrolizumab and nivolumab continued to show high rates of activity and durability.[8,9] There were patients with relapsed or refractory Hodgkin lymphoma who appear to have long-term disease control with pembrolizumab or nivolumab. The FDA approved nivolumab for relapsed/refractory classical Hodgkin lymphoma in May 2016. A similar approval is expected for pembrolizumab. These agents are finding a place among more standard therapy in the later-line relapsed/refractory setting and are being tested in earlier lines of therapy.

Brentuximab Vedotin Plus Nivolumab

Several ongoing studies are evaluating checkpoint inhibitors in earlier lines of therapy or as part of combinations. Dr Alex Herrera presented preliminary data for a phase 1/2 study of brentuximab vedotin plus nivolumab as second-line therapy in patients with relapsed or refractory classical Hodgkin lymphoma.[10] All the patients responded to treatment and were able to proceed directly to autologous stem cell transplant. Half of the patients had complete responses. Interestingly, in studies of single-agent brentuximab vedotin as a second-line therapy, only about a third of patients had complete or near-complete responses to brentuximab vedotin alone that allowed them to proceed directly to transplant without additional chemotherapy.[11,12]

This chemotherapy-free second-line regimen appears quite active. At this early stage, however, I would not recommend use of this approach off-study. It will be of interest to see how these data mature. There will likely be many additional follow-up studies evaluating ways to incorporate checkpoint inhibitors into earlier lines of therapy for Hodgkin lymphoma.

Relevant Disclosures

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