## Clinical Advances in HEMATOLOGY & ONCOLOGY A Peer-Reviewed Journal

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## A SPECIAL MEETING REVIEW EDITION

## Highlights in Lymphoma From the 2017 American Society of Hematology Annual Meeting and Exposition

A Review of Selected Presentations From the 2017 American Society of Hematology Annual Meeting and Exposition • December 9-12, 2017 • Atlanta, Georgia

## **Special Reporting on:**

- Brentuximab Vedotin Plus Doxorubicin, Vinblastine, and Dacarbazine as Frontline Therapy Demonstrates Superior Modified Progression-Free Survival Versus ABVD in Patients With Previously Untreated Stage III or IV Hodgkin Lymphoma: The Phase 3 ECHELON-1 Study
- Brentuximab Vedotin With R-CHP Chemotherapy as Frontline Treatment for Patients With CD30-Positive Primary Mediastinal Large B-Cell, Diffuse Large B-Cell, and Grey Zone Lymphomas: Results of a Phase I/II Multisite Trial
- In Vitro, In Vivo, and Parallel Phase I Evidence Support the Safety and Activity of Duvelisib, a PI3K-δ,γ Inhibitor, in Combination With Romidepsin or Bortezomib in Relapsed/Refractory T-Cell Lymphoma
- Results From a Phase 1/2 Study of Brentuximab Vedotin in Combination With Nivolumab in Patients With Relapsed or Refractory Hodgkin Lymphoma
- High Complete Response Rates With Pembrolizumab in Combination With Rituximab in Patients With Relapsed Follicular Lymphoma: Results of an Open-Label, Phase II Study
- Sequential Brentuximab Vedotin Before and After Adriamycin, Vinblastine, and Dacarbazine for Older Patients With Untreated Classical Hodgkin Lymphoma: Final Results From a Multicenter Phase II Study
- Nivolumab in Classical HL: Results From the Phase 2 CheckMate 205 Study

### **PLUS Meeting Abstract Summaries**

#### With Expert Commentary by:

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## ON THE WEB: hematologyandoncology.net

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## **NOW APPROVED** FOR pcALCL OR CD30-EXPRESSING MF ADULT PATIENTS AFTER PRIOR SYSTEMIC THERAPY

# **ADCETRIS:** SUPERIOR RESPONSE SUSTAINED FOR ≥4 MONTHS AND SUPERIOR PFS<sup>1,2</sup>

## **ORR4\*: Primary endpoint**<sup>1,2</sup>





COMPARATOR TREATMENT (METHOTREXATE OR BEXAROTENE) 95% Cl: 4.4, 20.6

\*ORR4: objective global response (complete or partial response) lasting at least 4 months

# Most common adverse reactions (≥10%) in patients treated with ADCETRIS<sup>®</sup> (brentuximab vedotin) • Anemia 62% • Fatigue 29% • Alopecia 15% • Asthenia 11%

- Peripheral sensory
- neuropathy 45%
- Nausea 36%
- Diarrhea 29%
- Neutropenia 21%
- Neutropenia 2
  Pruritus 17%
- Pyrexia 17%
- Vomiting 17%
- ronning r
- Decreased appetite 15%
- Thrombocytopenia 15%
- Arthralgia 12%
- Myalgia 12%

ADCETRIS 95% CI: 44.1, 68.4

- i i)digid i 270
- Dyspnea 11%
- Edema peripheral 11%
- Pruritus generalized 11%
- Rash maculo-papular 11%

## Most common serious adverse reactions in patients treated with ADCETRIS

- Cellulitis 3%
- Pyrexia 3%

### Indication

ADCETRIS<sup>®</sup> (brentuximab vedotin) is indicated for the treatment of adult patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have received prior systemic therapy.<sup>1</sup>

### Important Safety Information BOXED WARNING

#### PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML): JC virus infection resulting in PML and death can occur in

#### Contraindication

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

#### Warnings and Precautions

ADCETRIS-treated patients.

- Peripheral neuropathy (PN): ADCETRIS causes PN that is predominantly sensory. Cases of motor PN have also been reported. ADCETRISinduced PN is cumulative. Monitor for symptoms such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Institute dose modifications accordingly.
- Anaphylaxis and infusion reactions: Infusionrelated reactions (IRR), including anaphylaxis, have occurred with ADCETRIS. Monitor patients during infusion. If an IRR occurs, interrupt

the infusion and institute appropriate medical management. If anaphylaxis occurs, immediately and permanently discontinue the infusion and administer appropriate medical therapy. Premedicate patients with a prior IRR before 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 ADCETRIS dose. 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 ADCETRIStreated patients. Closely monitor patients during treatment for 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 use 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 use in patients with moderate or severe hepatic impairment.
- Hepatotoxicity: Serious cases, including fatal outcomes, have occurred in ADCETRIStreated patients. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, and occurred after the first ADCETRIS dose or rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may increase the risk. Monitor liver enzymes and bilirubin. Patients with new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCETRIS.
- 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, with some cases occurring within 3 months of initial exposure. Other possible contributory factors other than ADCETRIS include prior therapies and underlying disease that may cause immunosuppression. Consider PML diagnosis

# Superior PFS, with sustained separation from comparator treatment<sup>1,2</sup>

## PFS (key secondary endpoint)



PFS = progression-free survival HR = hazard ratio CI = confidence interval

ALCANZA: a global, open-label, multicenter, randomized trial in 131 patients with CD30-expressing mycosis fungoides (MF) or primary cutaneous anaplastic large-cell lymphoma (pcALCL) evaluating single-agent ADCETRIS vs physician's choice of methotrexate or bexarotene. Patients were randomized 1:1 and received either ADCETRIS 1.8 mg/kg intravenously every 3 weeks for up to 16 cycles (48 weeks) or physician's choice of methotrexate 5:50 mg orally once weekly or bexarotene 300 mg/m<sup>2</sup> orally once daily for up to 48 weeks. The primary endpoint was the rate of objective global response (complete or partial response) lasting at least 4 months (DRR4) as determined by an independent review facility (IRF). Progression-free survival (PFS) per IRF was a key secondary endpoint, calculated from randomization to date of disease progression or death (due to any cause).<sup>1</sup>

## See more breakthrough data at adcetrisupdate.com

in patients 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: Noninfectious pulmonary toxicity events including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome, some with fatal outcomes, have been reported. Monitor patients for signs and symptoms, 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: Acute pancreatitis, including fatal outcomes, has been reported. Other fatal and serious GI complications include perforation, hemorrhage, erosion, ulcer,

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intestinal obstruction, enterocolitis, neutropenic colitis, and ileus. Lymphoma with preexisting GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, including severe abdominal pain, perform a prompt diagnostic evaluation and treat appropriately.

• Embryo-fetal toxicity: Based on the mechanism of action and animal studies, ADCETRIS can cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus, and to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

#### **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

Moderate or severe hepatic impairment or severe renal impairment: MMAE exposure and adverse reactions are increased. Avoid use.

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, including BOXED WARNING, on following pages and full Prescribing Information at adcetrispro.com

References: 1. ADCETRIS [Prescribing Information]. Bothell, WA: Seattle Genetics, Inc.; November 2017. 2. Prince HM, Kim YH, Horwitz SM, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. *Lancet.* 2017;390:555-566.



#### 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.

#### 1 INDICATIONS AND USAGE

ADCTERIS is a CD30-directed antibody-conjugate indicated for treatment of adult patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30expressing mycosis fungoides (MF) who have received prior systemic therapy.

#### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dosage

Administer ADCETRIS as an intravenous infusion over 30 minutes every 3 weeks until a maximum of 16 cycles, disease progression, or unacceptable toxicity.

The recommended dose is 1.8 mg/kg up to a maximum of 180 mg. Reduce the dose in patients with mild hepatic impairment (Child-Pugh A) to 1.2 mg/kg up to a maximum of 120 mg. Avoid use in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or severe renal impairment (creatinine clearance [CrCL] <30 mL/ min). The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.

### 2.2 Dose Modification

**Peripheral Neuropathy:** For new or worsening Grade 2 or 3 peripheral neuropathy, hold dosing until improvement to baseline or Grade 1. Restart at 1.2 mg/kg up to a maximum of 120 mg. For Grade 4 peripheral neuropathy, the dosing should be discontinued. The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.

**Neutropenia:** For Grade 3 or 4 neutropenia, hold dosing until improvement to baseline or Grade 2 or lower. Consider G-CSF prophylaxis for subsequent cycles. In patients with recurrent Grade 4 neutropenia despite G-CSF prophylaxis, consider discontinuation or dose reduction to 1.2 mg/kg up to a maximum of 120 mg. The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.

#### 4 CONTRAINDICATIONS

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

#### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Peripheral Neuropathy

ADCETRIS treatment causes a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. ADCETRIS-induced peripheral neuropathy is cumulative.

In studies of ADCETRIS as monotherapy, 62% of patients experienced any grade of neuropathy. The median time to onset of any grade was 13 weeks (range, 0-52). Of the patients who experienced neuropathy, 62% had complete resolution, 24% had partial improvement, and 14% had no improvement at the time of their last evaluation. The median time from onset to resolution or improvement of any grade was 21 weeks (range, 0-195). Of the patients who reported neuropathy, 38% had residual neuropathy at the time of their last evaluation [Grade 1 (27%), Grade 2 (9%), Grade 3 (2%)].

Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Patients experiencing new or worsening peripheral neuropathy may require a delay, change in dose, or discontinuation of ADCETRIS.

#### 5.2 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, interrupt the infusion and institute appropriate medical management. Patients who have experienced a prior infusion-related reaction should be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.

#### 5.3 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. Monitor complete blood counts prior to each dose of ADCETRIS. Monitor more frequently 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.

#### 5.4 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. Monitor patients closely during treatment for the emergence of possible bacterial, fungal, or viral infections.

#### 5.5 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.

#### 5.6 Increased Toxicity in the Presence of Severe Renal Impairment

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

#### 5.7 Increased Toxicity in the Presence of Moderate or Severe Hepatic Impairment

The frequency of  $\geq$ Grade 3 adverse reactions and deaths was greater in patients with moderate and 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.

#### 5.8 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.

#### 5.9 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.

### 5.10 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.

#### 5.11 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.

#### 5.12 Gastrointestinal Complications

Acute pancreatitis, including fatal outcomes, has been reported. Other fatal and serious gastrointestinal (GI) complications include perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, neutropenic colitis, and ileus. Lymphoma with preexisting GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, including severe abdominal pain, perform a prompt diagnostic evaluation and treat appropriately.

#### 5.13 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 three 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.

#### 6 ADVERSE REACTIONS

#### 6.1 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.

Across the clinical trials of ADCETRIS as monotherapy (Studies 1-4), the most common adverse reactions (≥20%) in ADCETRIS-treated patients were peripheral sensory neuropathy, fatigue, nausea, diarrhea, neutropenia, upper respiratory tract infection, and pyrexia.

#### pcALCL and CD30-expressing MF (Study 4: ALCANZA)

ADCETRIS was studied in 131 patients with pcALCL or CD30-expressing MF requiring systemic therapy in a randomized, open-label, multicenter clinical trial in which the recommended starting dose and schedule was ADCETRIS 1.8 mg/kg intravenously over 30 minutes every 3 weeks or physician's choice of either methotrexate 5 to 50 mg orally weekly or bexarotene 300 mg/m<sup>2</sup> orally daily.

Of the 131 enrolled patients, 128 (66 brentuximab vedotin, 62 physician's choice) received at least one dose of study treatment. The median number of treatment cycles in the ADCETRIS-treatment arm was 12 (range, 1-16) compared to 3 (range, 1-16) and 6 (range, 1-16) in the methotrexate and bexarotene arms, respectively. Twenty-four (24) patients (36%) in the ADCETRIS-treatment arm received 16 cycles compared to 5 patients (8%) in the physician's choice arm.

Adverse reactions that led to dose delays in more than 5% of ADCETRIS-treated patients were peripheral sensory neuropathy (15%) and neutropenia (6%). Adverse reactions led to treatment discontinuation in 24% of ADCETRIS-treated patients. The most common adverse reaction that led to treatment discontinuation was peripheral neuropathy (12%). Serious adverse reactions were reported in 29% of ADCETRIS-treated patients. The most common serious adverse reactions were cellulitis (3%) and pyrexia (3%).

Table 7: Adverse Rea	actions Reported in ≥10%	<b>ADCETRIS-treated Patients with</b>
pcALCL or CD30-exp	pressing MF (Study 4: ALC	(ANZA)

		ADCETRI	S	Phys	ician's Cl	noicet
	n = 66 % of patients			n = 62 % of patients		
Adverse Reaction	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Blood and lymphatic system disorders						
Anemia*	62	-	-	65	5	-
Neutropenia*	21	3	2	24	5	-
Thrombocytopenia*	15	2	2	2	-	-
Nervous system disorders						
Peripheral sensory neuropathy	45	5	-	2	-	-
Gastrointestinal						
disorders						
Nausea	36	2	-	13	-	-
Diarrhea	29	3	-	6	-	-
Vomiting	17	2	-	5	-	-
General disorders and administration site conditions						
Fatigue	29	5	-	27	2	-
Pyrexia	17	-	-	18	2	-
Edema peripheral	11	-	-	10	-	-
Asthenia	11	2	-	8	-	2
Skin and subcutaneous tissue disorders						
Pruritus	17	2	-	13	3	-
Alopecia	15	-	-	3	-	-
Rash maculo-papular	11	2	-	5	-	-
Pruritus generalized	11	2	-	2	-	-
Metabolism and nutrition disorders						
Decreased appetite	15	-	-	5	-	-
Musculoskeletal and connective tissue disorders						
Arthralgia	12	-	-	6	-	-
Myalgia	12	-	-	3	-	-
Respiratory, thoracic and mediastinal disorders						
Dyspnea	11	-	-	-	-	-

\*Derived from laboratory values and adverse reaction data. †Physician's choice of either methotrexate or bexarotene.

Events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03.

## Additional Important Adverse Reactions

## Infusion reactions

In studies of ADCETRIS as monotherapy (Studies 1-4), 13% of ADCETRIS-treated patients experienced infusion-related reactions. The most common adverse reactions in Studies 1-4 ( $\geq$ 3% in any study) associated with infusion-related reactions were chills (4%), nausea (3-4%), dyspnea (2-3%), pruritus (2-5%), pyrexia (2%), and cough (2%). Grade 3 events were reported in 5 of the 51 ADCETRIS-treated patients who experienced infusion-related reactions.

### Pulmonary toxicity

In a trial in patients with cHL 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 (AETHERA), pulmonary toxicity was reported in 8 patients (5%) in the ADCETRIS-treated arm and 5 patients (3%) in the placebo arm.

### 6.2 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:* acute pancreatitis and 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.

#### 6.3 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in other studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Patients with cHL and systemic anaplastic large cell lymphoma (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 (62%) 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.

#### 7 DRUG INTERACTIONS

#### 7.1 Effect of Other Drugs on ADCETRIS

**CYP3A4 Inhibitors:** Co-administration of ADCETRIS with ketoconazole, a potent CYP3A4 inhibitor, increased exposure to MMAE, which may increase the risk of adverse reaction. Closely monitor adverse reactions when ADCETRIS is given concomitantly with strong CYP3A4 inhibitors.

**P-gp Inhibitors:** Co-administration of ADCETRIS with P-gp inhibitors may increase exposure to MMAE. Closely monitor adverse reactions when ADCETRIS is given concomitantly with P-gp inhibitors.

#### **USE IN SPECIFIC POPULATIONS** 8

## 8.1 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 [see Data]. Consider the benefits and risks of ADCETRIS and possible risks to the fetus when prescribing ADCETRIS to a pregnant woman.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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 cHL or sALCL who received the recommended dose of 1.8 mg/kg every three weeks.

### 8.2 Lactation

#### Risk Summary

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

#### 8.3 Females and Males of Reproductive Potential

ADCETRIS can cause fetal harm based on the findings from animal studies and the drug's mechanism of action.

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 ADCFTRIS

### 8.4 Pediatric Use

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

### 8.5 Geriatric Use

Clinical trials of ADCETRIS in cHL (Studies 1 and 3: AETHERA) and sALCL (Study 2) did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

In the clinical trial of ADCETRIS in pcALCL or CD30-expressing MF (Study 4: ALCANZA), 42% of ADCETRIS-treated patients were aged 65 or older. No meaningful differences in safety or efficacy were observed between these patients and younger patients.

#### 8.6 Renal Impairment

Avoid the use of ADCETRIS in patients with severe renal impairment (CrCL <30 mL/min). No dosage adjustment is required for mild (CrCL >50-80 mL/min) or moderate (CrCL 30-50 mL/min) renal impairment.

#### **Hepatic Impairment** 8.7

Avoid the use of ADCETRIS in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. Dosage reduction is required in patients with mild (Child-Pugh A) hepatic impairment.

#### OVERDOSAGE 10

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 17

#### Peripheral Neuropathy

Advise patients that ADCETRIS can cause a peripheral neuropathy. They should be advised to report to their health care provider any numbress 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.

#### Acute 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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## Brentuximab Vedotin Plus Doxorubicin, Vinblastine, and Dacarbazine as Frontline Therapy Demonstrates Superior Modified Progression-Free Survival Versus ABVD in Patients With Previously Untreated Stage III or IV Hodgkin Lymphoma: The Phase 3 ECHELON-1 Study

ore than 65,000 new cases of Hodgkin lymphoma are diagnosed annually worldwide, and approximately 40% are stage III or stage IV at presentation.<sup>1,2</sup> The chemotherapy combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) was originally developed in the 1970s and has been the standard of care for patients with Hodgkin lymphoma for decades.<sup>3,4</sup> However, ABVD is associated with major toxicities, including myelosuppression and pulmonary events that arise from the use of bleomycin. For patients who relapse after primary therapy, standard treatment consists of highdose chemotherapy plus autologous stem cell transplant.5,6 Brentuximab vedotin is an antibody-drug conjugate consisting of an antibody that binds to CD30 joined to monomethyl auristatin E by a protease-cleavable linker.7-10 After internalization, the monomethyl

auristatin E moiety is released and disrupts microtubule assembly. The combination of brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (AVD) was evaluated in a phase 1 dose-escalation trial.<sup>11,12</sup> The combination was generally well-tolerated and yielded a complete response (CR) rate of 96%, a 5-year failure-free survival rate of 92%, and a 5-year overall survival (OS) rate of 100%.

The open-label, randomized, phase 3 ECHELON-1 trial (Phase 3 Frontline Therapy Trial in Patients With Advanced Classical Hodgkin Lymphoma) evaluated the combination of brentuximab vedotin plus AVD vs ABVD as first-line therapy in patients with stage III/IV classical Hodgkin lymphoma.<sup>13,14</sup> Patients were randomly assigned to treatment with 6 cycles of ABVD or brentuximab vedotin (1.2 mg/kg on days 1 and 15) plus AVD. Imaging was performed following cycle

ABSTRACT SUMMARY Randomized Phase 2 Trial of Ofatumumab and Bendamustine Versus Ofatumumab, Bendamustine, and Bortezomib Induction and Maintenance Therapy in Patients With Previously Untreated High-Risk Follicular Lymphoma: Results From CALGB 50904 (Alliance)

The phase 2 Cancer and Leukemia Group B 50904 trial evaluated first-line of atumumab plus bendamustine, with or without bortezomib, in patients with high-risk follicular lymphoma (Abstract 485). Enrolled patients were randomly assigned to receive of atumumab plus bendamustine (arm A) or the same treatment plus bortezomib (arm B). After the first 6 cycles of treatment, patients received maintenance treatment every 8 weeks for 4 cycles, with bendamustine omitted. The ORR was 95% among the 66 patients in arm A vs 89% among the 63 patients in arm B, with CR rates of 59% vs 60%, respectively. There was no significant difference in PFS or OS. Two-year PFS was 80% for arm A vs 74% for arm B (*P*=.8088). OS was 96% vs 91%, respectively (*P*=.1505). No patient subgroup benefited from the addition of bortezomib. Rates of grade 3/4 toxicities were similar for both arms (67% to 69%).

2, after which patients with a Deauville score of 5 could be switched to the other treatment arm. The primary endpoint was modified progression-free survival (PFS) by independent review. This endpoint referred to the time to progression, death from any cause, or a position emission tomography scan showing a Deauville score of 3, 4, or 5 after completion of frontline therapy followed by additional anticancer therapy, whether or not there was a defined histologic progression. The secondary endpoint was OS.

The study enrolled 664 patients into the brentuximab vedotin plus AVD arm and 670 into the ABVD arm. Approximately one-third of the patients had stage III disease, 59% had B symptoms, 23% had bone marrow involvement, and 29% had more than 1 site of extranodal involvement. After a median follow-up of 24.9 months, the 2-year modified PFS rate by independent review was 82.1% (95% CI, 78.7%-85.0%) in the brentuximab vedotin plus AVD arm vs 77.2% (95% CI, 73.7%-80.4%) in the ABVD arm (hazard ratio [HR] for an event of progression, death, or modified progression, 0.77; 95% CI, 0.60-0.98; P=.035; Figure 1). Modified PFS was superior with the brentuximab vedotin combination among most subgroups, as evidenced by preplanned analysis. Interim analysis of OS was conducted at the same time as the primary endpoint, at which time 67 deaths had occurred (HR, 0.72; 95% CI, 0.44-1.17; P=.19). The final OS analysis will be conducted after 112 deaths.

The most common clinically important treatment-emergent adverse events (AEs) of any grade were neutropenia (58%), constipation (42%), and vomiting (33%) in the brentuximab



**Figure 1.** In the phase 3 ECHELON-1 trial, modified progression-free survival was higher with brentuximab vedotin plus AVD vs ABVD among patients with previously untreated stage III or IV Hodgkin lymphoma. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AVD, doxorubicin, vinblastine, and dacarbazine. Adapted from Connors JM et al. ASH abstract 6. *Blood.* 2017;130(suppl 1).<sup>13</sup>

vedotin plus AVD arm, and neutropenia (45%), constipation (37%), and fatigue (32%) in the ABVD arm. The most common AEs of grade 3 or higher in the brentuximab vedotin plus AVD arm were neutropenia, occurring in 54% (vs 39% in the ABVD arm), and febrile neutropenia, occurring in 19% (vs 8% in the ABVD arm). Among the 83 patients in the brentuximab vedotin plus AVD arm who received prophylactic treatment with granulocyte-colony simulating factor, the rate of febrile neutropenia was 11%, vs 21% among patients who did not receive prophylaxis (n=579). Peripheral neuropathy was observed in 67% of patients in the brentuximab vedotin plus AVD arm vs 43% in the ABVD arm. In the brentuximab vedotin arm, peripheral neuropathy had resolved completely or had improved by at least 1 grade in 67% of patients by the last follow-up visit. Interstitial lung disease of grade 3 or higher was observed in less than 1% of patients in the brentuximab vedotin plus AVD arm vs 3% of patients in the ABVD arm. Among

the 9 deaths that occurred in the brentuximab vedotin plus AVD arm, 7 were associated with neutropenia. Eleven of 13 deaths in the ABVD arm were related to pulmonary toxicity.

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## Brentuximab Vedotin With R-CHP Chemotherapy as Frontline Treatment for Patients With CD30-Positive Primary Mediastinal Large B-Cell, Diffuse Large B-Cell, and Grey Zone Lymphomas: Results of a Phase I/II Multisite Trial

D30 is expressed in approximately 20% of diffuse large B-cell lymphomas (DLBCLs), 80% of primary mediastinal large B-cell lymphomas (PMBLs), and 100% of gray zone lymphomas. PMBL is a rare form of lymphoma with molecular and clinical features that resemble classical Hodgkin lymphoma.1 Current firstline regimens include rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), with or without radiation; and doseadjusted etoposide and doxorubicin, plus cyclophosphamide, vincristine, prednisone, and rituximab (DA-EPOCH-R).<sup>2,3</sup> With R-CHOP, rates of event-free survival and PFS are less than 80%, and most patients receive treatment with radiation, which is associated with long-term negative effects.<sup>3,4</sup> DA-EPOCH-R is an intense, infusional regimen, and real-world and pediatric data have shown lower PFS rates compared with the initial study by Dunleavy and colleagues.<sup>2,5-7</sup>

Brentuximab vedotin has shown activity in patients with relapsed or refractory PMBL and was evaluated as first-line treatment in combination with rituximab plus cyclophosphamide, doxorubicin, and prednisone (R-CHP) in a phase 1/2 study.<sup>8-10</sup> Eligible patients had treatment-naive, histologically confirmed, CD30-positive PMBL, DLBCL, or gray zone lymphoma of any stage and an Eastern Cooperative Oncology Group (ECOG) performance status ranging from 0 to 3. Brentuximab vedotin was administered at 1.8 mg/kg concurrently with R-CHP on day 1, once every 3 weeks for 6 cycles. Responses were measured via fluorodeoxyglucose positron emission tomography (FDG-PET)/computed tomography (CT). Granulocyte-colony stimulating factor was allowed, and consolidative radiation was permitted after posttreatment imaging.

The 31 patients had a median age of 37 years (range, 18-76 years), and 42% had stage III/IV disease. Among the 23 patients with PMBL, 91% had bulky tumors that were 7.5 cm or longer. Grade 3/4 AEs that were possibly related to study treatment were observed in 87% of patients. They included hematologic events (reported in 74% of patients) and nonhematologic events (in 35%). Grade 3 febrile neutropenia was observed in 23% of patients. Two patients discontinued treatment. A reduction in the dose of brentuximab vedotin was required in 2 patients owing to AEs. One patient developed acute myeloid leukemia at 2 years after completion of therapy. Among 6 patients treated with brentuximab vedotin in combination with R-CHP, no dose-limiting toxicities were observed.

The dose was expanded for the



**Figure 2.** Progression-free survival among patients treated with brentuximab vedotin and R-CHP as frontline treatment. DLBCL, diffuse large B-cell lymphoma; GZL, gray zone lymphoma; PMBL, primary mediastinal large B-cell lymphoma; R-CHP, rituximab plus cyclophosphamide, doxorubicin, and prednisone. Adapted from Svoboda J et al. ASH abstract 191. *Blood.* 2017;130(suppl 1).<sup>10</sup>

phase 2 portion of the study. Among 29 patients in the phase 1/2 study population, the overall response rate (ORR) was 100%, with a CR rate of 86%. All of the PRs occurred in patients with PMBL. After a median follow-up of 17 months (range, 7-44 months), median PFS and median OS were not reached (Figure 2). The 1-year PFS was 92% (95% CI, 73%-98%), and 1-year OS was 100%. In the cohort of 22 PMBL patients, median PFS and median OS were also not reached. At 1 year, PFS was 89% (95% CI, 64%-97%) and OS was 100%. No differences were observed between the 14 patients who received radiotherapy and the 8 patients who did not (P=.47). The PMBL patients showed a high rate of thromboembolic events, including deep vein thrombosis (23%) and pulmonary embolism (14%).

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## ABSTRACT SUMMARY A Pilot Study of Brentuximab Vedotin and AVD Chemotherapy Followed By 20 Gy Involved-Site Radiotherapy in Early-Stage, Unfavorable-Risk Hodgkin Lymphoma

A pilot study was conducted in patients with stage I or II, unfavorable-risk Hodgkin lymphoma to evaluate brentuximab vedotin plus AVD followed by siteinvolved radiation therapy (Abstract 734). Patients were treated with 2 cycles of brentuximab vedotin (1.2 mg/kg) plus AVD followed by imaging and 2 more cycles of brentuximab vedotin plus AVD. Growth-factor support was mandatory. Patients were divided into 4 cohorts based on risk features. Patients in cohorts 1 and 3 received 30 Gy radiation therapy, those in cohort 2 received 20 Gy, and those in cohort 4 received no radiation therapy. Patients in cohort 1 had a 1-year PFS of 93% (95% Cl, 84%-100%), with no relapses after a median follow-up of 34 months (Kumar A et al. *Blood*. 2016;128[11]:1458-1464). Among the 28 patients in cohort 2, the CR rate was 100%. No relapses occurred after a median follow-up of 19 months. One patient died in a car accident. The 1-year PFS was 96% (95% Cl, 90%-100%).

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## In Vitro, In Vivo, and Parallel Phase I Evidence Support the Safety and Activity of Duvelisib, a PI3K- $\delta$ , $\gamma$ Inhibitor, in Combination With Romidepsin or Bortezomib in Relapsed/Refractory T-Cell Lymphoma

uvelisib is an oral inhibitor of phosphoinositide 3-kinase (PI3K) delta and PI3Kgamma that has shown encouraging efficacy in a phase 1 study, with ORRs of 50% in peripheral T-cell lymphoma and 32% in cutaneous T-cell lym-

phoma.<sup>1</sup> Responses have been linked to constitutive activation of phosphorylated Akt in T-cell lymphoma cell lines (P=.024). Based on its encouraging activity in T-cell lymphoma, duvelisib was evaluated in combination with romidepsin or bortezomib in 2 parallel phase 1 studies in patients with relapsed or refractory peripheral or cutaneous T-cell lymphoma.<sup>2</sup> The studies followed a 3 + 3 design with dose expansion at the maximum tolerated dose. A lead-in cohort of patients treated with duvelisib monotherapy prior to the combination



**Figure 3.** Treatment-related adverse events among patients with relapsed/refractory T-cell lymphoma treated with duvelisib plus romidepsin in a phase 1 trial. The figure shows events affecting  $\geq$ 20% of patients and all grade 3/4 events. Adapted from Moskowitz A et al. ASH abstract 819. *Blood.* 2017;130(suppl 1).<sup>2</sup>

was included to learn more about this agent's mechanism of action and to improve patient selection.

In arm A, duvelisib was administered twice daily at 25 mg, 50 mg, or 75 mg in combination with romidepsin. No dose-limiting toxicities were observed, and the maximum tolerated dose was established as romidepsin at 10 mg/m<sup>2</sup> on days 1, 8, and 15 plus duvelisib at 75 mg twice daily. Across all cohorts, the most common AEs observed with the combination treatment were grade 1/2 fatigue, nausea, and altered taste (Figure 3). The most common grade 3/4 event was neutropenia. Two deaths occurred that were unrelated to study treatment, including 1 from diffuse alveolar hemorrhage following allogeneic stem cell transplant and 1 from sepsis in the setting of disease progression. Across the 3 dose cohorts, 9 patients (60%) achieved a response. CRs occurred in 4 patients (27%) and PRs in 5 (33%). PRs were observed in 2 of 4 patients with cutaneous T-cell lymphoma

(50%). Among the 11 patients with peripheral T-cell lymphoma, 7 achieved a response (64%), including 4 CRs (36%) and 3 PRs (27%).

In arm B, duvelisib was administered twice daily at 25 mg, 50 mg, or 75 mg in combination with bortezomib. One patient experienced a dose-limiting toxicity of pneumonia at the lowest duvelisib dose level, and the maximum tolerated dose was identified as duvelisib at 25 mg, twice daily, plus bortezomib at 1.0 mg/m<sup>2</sup> on days 1, 4, 8, and 11. Across all cohorts, the most common treatment-related AE of any grade was diarrhea/colitis, observed in 12 of 17 patients (71%). The most common treatment-related grade 3/4 AE was elevated levels of alanine and/ or aspartate transaminase, observed in 6 patients (35%), followed by high alkaline phosphatase levels, rash, and neutropenia, each observed in 2 patients (12%). Serious grade 3/4 AEs occurred in patients treated with the higher doses of duvelisib, leading to expansion with the lowest-dose combination. One death occurred in a patient who developed Stevens-Johnson syndrome. Among 17 patients treated in the 3 dose cohorts, 6 (35%) achieved a response, half of which were CRs. Among 7 patients with cutaneous T-cell lymphoma, only 1 patient (14%) achieved a PR. There were no CRs. Among 10 patients with peripheral T-cell lymphoma, the ORR was 50% and included 3 patients with CRs.

The rate of liver function abnormalities was higher with duvelisib plus bortezomib compared with duvelisib plus romidepsin. Similarly, a previous study of duvelisib monotherapy in 210 patients showed high rates of abnormal liver function.<sup>3</sup> Elevated alanine aminotransferase of any grade was observed in 39% of patients treated with duvelisib alone, including 20% with grade 3/4 elevations. Elevated aspartate transaminase of any grade was observed in 38% of patients, including 15% with grade 3/4 elevations. In contrast, among the 16 patients treated with duvelisib and romidepsin, grade 1/2 elevations in alanine or aspartate transaminase each occurred in 13% of patients, with no grade 3/4 elevations. The addition of romidepsin to duvelisib appeared to confer a protective effect with regard to toxicity. Further expansion of the duvelisib plus romidepsin cohort is planned.

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

ivolumab and brentuximab vedotin have demonstrated single-agent activity among patients with relapsed or refractory Hodgkin lymphoma.<sup>1,2</sup> A study was conducted to evaluate the combination of brentuximab vedotin plus nivolumab as an alternative to chemotherapy in patients with relapsed or refractory Hodgkin lymphoma.<sup>3</sup> The open-label, multicenter, phase 1/2 trial enrolled 62 adults with relapsed or refractory classical Hodgkin lymphoma after first-line chemotherapy. Responses were assessed using the 2014 Lugano classification.<sup>4</sup> The primary endpoints were safety, including AE incidence and severity, and the CR rate following completion of study treatment. Patients received treatment every 3 weeks for up to 4 cycles. For cycle 1, patients received brentuximab vedotin on day 1 and nivolumab on

day 8, with both therapies administered on day 1 for subsequent cycles. Blood samples for biomarker analyses were taken throughout the study and at the end of treatment. After completing the end-of-treatment response assessment, patients were eligible for autologous stem cell transplant. AEs were recorded from the start of treatment through 100 days after the last dose of nivolumab.

The 62 enrolled patients had a median age of 36 years (range, 18-69 years), and 39% had stage III/IV disease. Sixty-one patients received at least 1 dose of the study drug, and 58 patients completed all 4 cycles of brentuximab vedotin plus nivolumab. There were 4 treatment discontinuations during the study: 2 based on patient decisions not involving an AE, 1 owing to grade 3 peripheral neuropathy, and 1 owing to the inves-

tigator's decision. Nearly all patients experienced an AE of any grade, and 31% had an AE of grade 3 or higher. The most common AEs of any grade were nausea (49%), infusion-related reactions (44%), and fatigue (41%). Grade 3 AEs occurred in 17 patients (28%). Grade 4 AEs were observed in 2 patients (3%), including 1 case each of thrombocytopenia and increased lipase enzymes.

Infusion-related reactions occurred in 27 patients (44%), including 25 patients (41%) who experienced a reaction during infusion with brentuximab vedotin. Pretreatment with a low-dose corticosteroid and an antihistamine did not affect the frequency or severity of infusion-related reactions. Although no patient discontinued treatment owing to an infusion-related reaction, the event led to interruption of the infusion in 26 patients (26%).



**Figure 4.** Change in  $SUV_{max}$  from baseline among patients with relapsed or refractory Hodgkin lymphoma treated with brentuximab vedotin plus nivolumab. SUV, standardized uptake value. Adapted from Herrera AF et al. ASH abstract 649. *Blood.* 2017;130(suppl 1).<sup>1</sup>

Excluding any infusion-related reactions, potential immune-related AEs occurred in 50 patients (82%). Five patients were treated with a systemic corticosteroid for an immune-related AE; these cases consisted of grade 4 colitis and grade 4 pneumonitis, grade 4 pneumonitis, grade 3 diarrhea and grade 2 colitis, grade 3 transaminase elevation, and grade 2 pneumonitis. AEs did not lead to any treatment discontinuations.

Among 60 patients evaluable for efficacy, the ORR was 83% (95% CI, 72%-92%). The CR rate was 62% (95% CI, 48%-74%). Patients with a Deauville score of 1 or 2 accounted for 29 of the CRs (78%). One patient with a Deauville score of 5 achieved a CR. Among the 13 patients (22%) with a PR (95% CI, 12%-34%), all had a Deauville score of 4 or 5. Among the 60 patients who were evaluable for efficacy, 54 ultimately proceeded to autologous stem cell transplant, including 42 who proceeded to transplant directly after completing study treatment and 12 who proceeded to transplant after receiving subsequent salvage therapy. Treatment with brentuximab vedotin and nivolumab did not appear to affect yields of stem cell mobilization and collection or engraftment. After a median followup of 8 months, the median duration of response was not reached. Sixmonth PFS was 89% (95% CI, 75%-95%). The changes in standardized uptake value are shown in Figure 4.

Populations of T cells decreased after administration of brentuximab vedotin and increased after administration of both brentuximab vedotin and nivolumab, with the most dramatic changes in cell count observed for T-regulatory cells (Figure 5). The activated and dividing CD4-positive T-cell populations followed a similar pattern, decreasing after infusion of brentuximab vedotin on day 1 of cycle 1, and then significantly increasing after administration of both antibodies during cycle 2. Although T-cell receptor clonality did not change with dual



**Figure 5.** Among the T-cell subsets, Tregs showed the greatest decrease after administration of brentuximab vedotin and the greatest increase after administration of brentuximab vedotin plus nivolumab (arrows). BSLN, baseline; EOT, end of treatment. Tregs, T-regulatory cells. Adapted from Herrera AF et al. ASH abstract 649. *Blood.* 2017;130(suppl 1).<sup>3</sup>

antibody treatment, preexisting T-cell clones in the periphery expanded. After patients received brentuximab vedotin on day 1 of cycle 1, cytokine and chemokine profiles were consistent with innate immune system activation. In contrast, after coadministration of both antibodies on day 1 of cycle 2, the cytokine and chemokine profile was consistent with activation of the adaptive immune response. Baseline levels of interferon-gamma inducible protein 10 were significantly lower in patients who achieved a CR (P=.0178). Thymus- and activation-regulated chemokine levels were also lower in patients who achieved a CR, both at baseline and afterward. According to ex vivo testing of peripheral blood samples with major histocompatibility complex 1 and 2 antigen peptides, there was an increase in interferon-gamma expression from effector memory CD8-positive T cells. The greatest stimulation was observed at day 15 of cycle 1, which is consistent with

activation of the immune system after treatment with both antibodies.

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## High Complete Response Rates With Pembrolizumab in Combination With Rituximab in Patients With Relapsed Follicular Lymphoma: Results of an Open-Label, Phase II Study

umors associated with follicular lymphoma are infiltrated with antitumor T cells. These T cells are functionally impaired, however, owing to PD-1 expression and pathway activation, and the tumor cells continue to reproduce.1 Pembrolizumab is an anti-PD-1 antibody that restores antitumor T-cell function, and rituximab is an anti-CD20 antibody that induces tumor cell killing through antibody-directed cellular cytotoxicity. Combining these antibodies could provide synergistic antitumor activity by activating both the innate and adaptive immune systems. The combination of pembrolizumab and rituximab was evaluated in an open-label, 1-arm, single-institution, phase 2 trial of adults with grade 1 to 3a follicular lymphoma who had rituximab-sensitive disease and had relapsed after treatment with at least 1 prior therapy.<sup>2</sup> Eligible patients had an ECOG performance status of 0 to 1.

Patients were treated with 4 weekly doses of ruxolitinib at 375 mg/m<sup>2</sup> on days 1, 8, 15, and 22. Treatment with pembrolizumab began on day 2 in a flat dose of 200 mg, and was continued every 3 weeks for up to 16 doses. Responses were assessed according to the Lugano Classification.<sup>3</sup> The primary objective was ORR. It was anticipated that the 2-drug combination would improve ORR to 60%, from the 40% seen with rituximab monotherapy in historical controls.

The 30 evaluable patients had a median age of 64 years (range, 43-84 years), and 57% were male. The Follicular Lymphoma International Prognostic Index (FLIPI) score was low in 27% of patients, intermediate in 53%, and high in 20%. Sixty percent of patients had stage IV disease. The median PFS from the most recent prior line of therapy was 28 months (range, 3-162 months).

After a median follow-up of 13.8

## ABSTRACT SUMMARY Anti-CCR4 Monoclonal Antibody, Mogamulizumab, Demonstrates Significant Improvement in PFS Compared to Vorinostat in Patients With Previously Treated Cutaneous T-Cell Lymphoma: Results From the Phase 3 MAVORIC Study

Mogamulizumab is a first-in-class defucosylated, humanized antibody against C-C chemokine receptor type 4 (CCR4). The open-label, randomized MAVORIC study (Study of KW-0761 Versus Vorinostat in Relapsed/Refractory CTCL) compared mogamulizumab vs vorinostat in patients with previously treated, stage IB to IVB mycosis fungoides or Sézary syndrome (Abstract 817). The study enrolled 372 patients at 61 centers across 11 countries. The patients had a median age of 64 years (range, 25-101 years), and nearly all had an ECOG performance status of 0 or 1. Approximately 55% of patients had mycosis fungoides. The study achieved its primary endpoint of improved PFS. The median PFS was 7.7 months with mogamulizumab vs 3.1 months with vorinostat (HR, 0.53; 95% CI, 0.41-0.69; P<.0001). The ORR was 28% vs 5%, respectively (P<.05). Rates of infusion-related reactions and drug eruptions were higher in the mogamulizumab arm, but the safety profile was manageable.

months, the antibody combination yielded an ORR of 67%, with a CR rate of 50% (Figure 6). The median duration of response was 14.1 months. The median PFS was 11.4 months. In patients who experienced a PFS lasting beyond 1 year with their most recent therapy, median PFS was 13.8 months (95% CI, 8.5 months to not reached), whereas for patients who had experienced a PFS lasting 1 year or less, the median PFS with the antibody combination was 4.1 months.

The most common treatmentemergent AEs of any grade were fatigue (46%), diarrhea (40%), and nausea and vomiting (37%). Grade 3/4 AEs included nausea and vomiting (7%), diarrhea (3%), and transaminitis (3%). In addition, 1 patient (3%) experienced grade 3 aseptic meningitis. Six patients discontinued treatment owing to immune-related AEs, including grade 2/3 diarrhea (10%), grade 2 pneumonitis (7%), and grade 2 rash (3%).

Programmed death ligand 1 (PD-L1) was detected in the histiocytes of the 19 tumors tested. However, PD-L1 was not detected on tumor cells in 8 samples. Among the latter, 50% of patients responded, yielding 2 CRs and 2 PRs. Among the 11 tumor samples with PD-L1 expression, PD-L1 was present in 1% to 8% of tumor cells in 10 samples and in 20% of tumor cells in 1 sample. PD-L1 expression was not a significant predictor of response (P=.71). Analysis of immune cell gene signatures in baseline tumors of 18 patients showed an association between the presence of a high CD8positive T-effector score and a CR.

For the overall study population, the ORR was 67% for patients with a high CD8-positive T-effector score and 63% in those with a low score.



**Figure 6.** Responses among patients with relapsed follicular lymphoma treated with pembrolizumab in combination with rituximab. <sup>a</sup>Patients with an early relapse (<24 months) after frontline treatment. Adapted from Nastoupil L et al. ASH abstract 414. *Blood*. 2017;130(suppl 1).<sup>2</sup>

For patients who achieved a CR, 67% had a high score and 28% had a low score. Interferon-gamma has been proposed as a biomarker associated with response to pembrolizumab.<sup>4</sup> Peripheral blood samples were available from 26 patients who received treatment with pembrolizumab plus rituximab. Among these patients, interferon-gamma–related scores correlated with response to the 2-drug combination based on a 10-gene score (*P*=.016) and a 28-gene score (*P*=.023).

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## Sequential Brentuximab Vedotin Before and After Adriamycin, Vinblastine, and Dacarbazine for Older Patients With Untreated Classical Hodgkin Lymphoma: Final Results From a Multicenter Phase II Study

Patients with Hodgkin lymphoma ages 60 years and older are consistently underrepresented in clinical trials, and their outcomes are inferior to those seen in younger patients.<sup>1,2</sup> In a prospective study that compared ABVD vs the Stanford V regimen in Hodgkin lymphoma, elderly patients had a sig-

nificantly reduced 5-year failure-free survival (74% vs 48%; P=.002) and OS (90% vs 58%; P<.0001) compared with younger patients.<sup>3</sup> In a study of 27 elderly patients with Hodgkin lymphoma (median age, 78 years), first-line treatment with brentuximab vedotin monotherapy yielded an ORR of 92% and a CR rate of 73%.<sup>4</sup> However, 30% of the patients experienced grade 3 neuropathy and lost the ability to perform daily activities, such as bathing and eating. The median PFS was 10.5 months for all patients vs 11.8 months for patients who achieved a CR. Combining brentuximab vedotin with dacarbazine or bendamustine led to a longer median PFS of 17.94



**Figure 7.** Survival in the intent-to-treat population of a trial evaluating sequential brentuximab vedotin before and after AVD among elderly patients with Hodgkin lymphoma. AVD, doxorubicin, vinblastine, and dacarbazine. Adapted from Evens AM et al. ASH abstract 733. *Blood.* 2017;130(suppl 1).<sup>6</sup>

## ABSTRACT SUMMARY Pralatrexate in Combination With Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP) in Previously Untreated Patients With Peripheral T-Cell Lymphoma (PTCL): A Phase 1 Dose-Escalation Study

The combination of pralatrexate plus CHOP every 21 days was investigated as first-line treatment in patients with peripheral T-cell lymphoma in a phase 1, dose-escalation study (Abstract 818). Pralatrexate was administered in doses ranging from 10 mg/m<sup>2</sup> to 30 mg/m<sup>2</sup> on days 1 and 8. Enrolled patients had histologically confirmed peripheral T-cell lymphoma, had not received systemic therapy for the disease, and had an ECOG performance status of 0 to 2. The 31 patients had a median age of 57.7 years (range, 18-78 years), and 64.5% were male. The majority (58.1%) had peripheral T-cell lymphoma not otherwise specified. One dose-limiting toxicity of creatinine elevation was observed at the highest pralatrexate dose level. Pralatrexate at 30 mg/m<sup>2</sup> was chosen for the expansion cohort, AEs leading to discontinuation occurred in 11.1% of patients, and grade 3/4 AEs occurred in 78%. Across all cohorts, the ORR was 90% (95% Cl, 72.7%-97.8%), with a CR rate of 66%.

months.<sup>5</sup> The ORR was 100% and the CR rate was 62%. However, the PFS for patients with a CR was only 10.78 months. Grade 3 neuropathy occurred in 27% of patients, and 2 patients died from toxicity.

An investigator-initiated study evaluated the incorporation of brentuximab vedotin into frontline therapy followed by AVD in elderly patients with Hodgkin lymphoma.<sup>6</sup> Eligible patients were ages 60 years or older and had treatment-naive, advancedstage Hodgkin lymphoma. Enrolled patients initially received 2 cycles of brentuximab vedotin (1.8 mg/kg every 3 weeks) and then 6 cycles of AVD, followed by 4 cycles of brentuximab vedotin consolidation. The study used a Simon 2-stage design, with a planned enrollment of 48 patients. The primary endpoint was the CR rate after AVD treatment. Responses were assessed using the Lugano criteria based on FDG-PET/CT with Deauville criteria.<sup>7</sup> Benchmarks for evaluating the CR rate ranged from 46% to 78%.<sup>3,8,9</sup>

The 48 patients had a median age of 69 years (range, 60-88 years), and 63% were male. One-fourth of patients had classical Hodgkin lymphoma histology. Eighty-two percent of patients had stage III/IV disease, 23% had bone marrow involvement, and the median Cumulative Illness Rating score was 6. Among 7 patients who were not evaluable for response after the final AVD cycle, 1 died from pancreatitis,10 4 withdrew owing to toxicities (2 each from brentuximab vedotin induction or AVD in cycle 1), and 2 patients withdrew consent, both owing to diarrhea from brentuximab vedotin induction. The median Cumulative Illness Rating score of these 7 patients was 13 (range, 10-19) vs 5 (range, 0-20) for the evaluable patients (P=.001).

After 2 cycles of brentuximab vedotin and 6 cycles of AVD, the ORR in 41 evaluable patients was 95%, with a CR rate of 90%. The CR rate increased to 93% after 4 cycles of brentuximab vedotin consolidation. In the intent-to-treat population of 48 patients, the ORR was 88%, with a CR rate of 81% after the final AVD treatment cycle.

Serious AEs were observed in 42% of patients. Grade 2 peripheral neuropathy occurred in 33% of patients, but most cases were reversible. The most common grade 3/4 serious AE was infection (15%). Only 4% of patients experienced grade 3/4 peripheral neuropathy. Approximately half of patients (52%) completed all treatment cycles. Discontinuation was attributed to withdrawal of consent in 9% and no response or progressive disease in 6%. A total of 33% of patients withdrew from the study owing to toxicity, including grade 2 peripheral neuropathy in 12%.

After a median follow-up of 31 months, the intent-to-treat population had a 2-year PFS of 85% and a 2-year OS of 94% (Figure 7). The univariate analysis showed that increasing age, female sex, and increasing Cumulative Illness Rating score corresponded to inferior PFS ( $P \le .05$  for each). Multivariate analysis showed that increasing age after 60 years was associated with an inferior PFS (HR, 1.19 for each year; 95% CI, 1.02-1.37; P=.02).

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ABSTRACT SUMMARY PET-Based Response After 2 Cycles of Brentuximab Vedotin in Combination With AVD for First-Line Treatment of Unfavorable Early-Stage Hodgkin Lymphoma: First Analysis of the Primary Endpoint of BREACH, a Randomized Phase 2 Trial of LYSA-FIL-EORTC Intergroup

The BREACH study (Brentuximab Vedotin Associated With Chemotherapy in Untreated Patients With Hodgkin Lymphoma) is an open-label, multicenter, international, randomized phase 2 trial investigating PET-based response after 2 cycles of brentuximab vedotin plus AVD in patients with treatment-naive, unfavorable, stage I/II Hodgkin lymphoma (Abstract 736). Patients were ages 18 to 60 years and had at least 1 unfavorable disease characteristic. They were randomly assigned to receive 4 cycles of standard ABVD or 4 cycles of brentuximab vedotin (1.2 mg/kg given every 2 weeks) plus AVD, followed by radiotherapy (30 Gy). Patients were evaluated by PET/CT at baseline and after cycles 2 and 4. After 2 treatment cycles, 93 of 113 patients in the brentuximab vedotin arm (82.3%) were PET-negative vs 43 of 57 patients in the control arm (75.4%), meeting the primary objective. During the first 2 cycles, the brentuximab vedotin regimen was associated with increased toxicity compared with ABVD.

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## Nivolumab in Classical HL: Results From the Phase 2 CheckMate 205 Study

In the phase 2 CheckMate 205 study, patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant received treatment with nivolumab (3 mg/kg every 2 weeks).<sup>1,2</sup> The trial yielded an ORR of 69%, with durable responses, an acceptable safety profile, and a potential benefit

in patients with stable or progressive disease. Studies of checkpoint inhibitors suggested that some patients with solid tumors may benefit from treatment after disease progression.<sup>3,4</sup> As a result, the CheckMate 205 study was amended in July 2014 to allow patients with stable performance status and perceived clinical benefit to receive treatment beyond investigator-assessed disease progression.

The CheckMate 205 trial enrolled 243 patients with an ECOG performance status of 0 or 1 who required treatment after autologous stem cell transplant. The 63 patients in cohort A had no prior exposure to brentuximab vedotin. The 80 patients in cohort B



**Figure 8.** Probability of survival in the CheckMate 205 trial among patients with relapsed/refractory classical Hodgkin lymphoma treated with nivolumab after autologous stem cell transplant. OS, overall survival; PGF, progression-free patients; TBP, treated beyond investigator-assessed disease progression. Adapted from Cohen JB et al. ASH abstract 650. *Blood.* 2017;130(suppl 1).<sup>6</sup>

had received brentuximab vedotin after autologous stem cell transplant. The 100 patients in cohort C had received brentuximab vedotin at some point for relapsed disease. Cohort D included 51 patients with newly diagnosed, advanced-stage classical Hodgkin lymphoma, and these patients were treated with nivolumab plus AVD.5 Disease progression occurred in 105 patients in cohorts A, B, and C. Among these patients, 70 were treated beyond disease progression and the remaining 35 were not.<sup>6</sup> Patients were permitted to receive treatment beyond disease progression until they experienced an increase in overall tumor burden of 10% or more.

The 70 patients in the treatmentbeyond-progression group had a median age of 37 years (range, 18-72 years), 67% were male, and 61% had an ECOG performance status of  $0.^6$ The 35 patients who progressed and did not receive further treatment had a median age of 34 years (range, 23-63 years), 54% were male, and 34% had an ECOG performance status of 0. B symptoms were present in 20% of patients who received treatment beyond progression vs 34% of patients who did not receive treatment after progression. The most common cause of progression in the treatment-beyondprogression group was development of a new lesion (reported in 67%). Patients in the treatment-beyondprogression group received a median of 8 doses of nivolumab (range, 1-43 doses) after initial progression, and the median follow-up after initial progression was 4 months (range, <1-17 months). The rate of treatment-related AEs was similar in the treatmentbeyond-progression group before and after progression. Drug-related AEs of any grade were observed in 64% of patients before progression and in

46% of patients afterward. These drugrelated AEs were grade 3 or 4 in 9% vs 13%, respectively.

Before initial disease progression, the responses in the treatmentbeyond-progression group included a CR rate of 7% and a PR rate of 44%.6 Stable disease was reported in 29% of patients, and 19% had progressive disease. (Responses were not evaluable in 1%.) Among patients who were not treated beyond progression, the CR rate was 23%, the PR rate was 34%, 26% had stable disease, 11% had progressive disease, and 6% were not evaluable. Among 51 patients in the treatment-beyond-progression group who were evaluable for response to treatment after initial disease progression, 53% showed some reduction in target lesions: 31% had a reduction of more than 25%, 14% had a reduction of more than 50%, and 2% had a reduction of 100%. The time from



**Figure 9.** Response in the CheckMate 205 trial among newly diagnosed patients with classical Hodgkin lymphoma treated with nivolumab. Data for the intent-to-treat population are shown. Responses were assessed according to criteria from the International Working Group. Some values do not total the ORR owing to rounding. INV, investigator review; IRC, independent review committee; ORR, overall response rate. Adapted from Ramchandren R et al. ASH abstract 651. *Blood.* 2017;130(suppl 1).<sup>5</sup>

initial progression to next therapy was 8.8 months (95% CI, 5.5 months to not reached) in the treatment-beyondprogression group vs 1.5 months (95% CI, 0.6-3.3 months) in the nontreatment-beyond-progression group. Twelve-month OS was 93% (95% CI, 83%-97%) vs 80% (95% CI, 62%-90%), respectively (Figure 8).

The 51 patients in cohort D of

the CheckMate 205 study were adults with newly diagnosed classical Hodgkin lymphoma of stage IIB, III, or IV.<sup>5</sup> They had an ECOG performance status of 0 or 1. Patients initially received 4 doses of nivolumab (240 mg given every 2 weeks) followed by continued nivolumab plus AVD every 2 weeks. Patients had a median age of 18 years (range, 18-87 years), and 63% were

## ABSTRACT SUMMARY Phase II Study of Brentuximab Vedotin Plus Ibrutinib for Patients With Relapsed/Refractory Hodgkin Lymphoma

The combination of brentuximab vedotin plus ibrutinib was evaluated in a prospective, phase 2 trial of patients with relapsed or refractory Hodgkin lymphoma (Abstract 738). Patients were treated with brentuximab vedotin at 1.8 mg/kg every 3 weeks and ibrutinib at 560 mg/day. Three patients in the lead-in cohort received ibrutinib at 420 mg/day. The study enrolled 16 patients, with a minimum age of 15 years. Their median age was 33 years (range, 17-69 years), 50% had stage III/IV disease, and 50% had refractory disease. Patients received a median of 4 cycles (range, 2-9) of treatment. The ORR was 75%. The CR rate and PR rate were each 37%. Among 13 patients treated with ibrutinib at 560 mg, the ORR was 84.6%, with a CR rate of 46%. The most common AEs of grade 2 or higher were rash (25%), neutropenia (19%), infusion reaction (19%), and hypophosphatemia (19%). Two patients (13%) experienced grade 3 neutropenia, and 1 (6%) developed grade 3 colitis. male. B symptoms at diagnosis were reported in 80% of patients, 31% had bulky disease, and 49% had extranodal involvement.

More than half of patients experienced grade 3/4 treatment-related hematologic AEs, most commonly, grade 3/4 neutropenia (49%).<sup>5</sup> Grade 3/4 nonhematologic treatment-related AEs included nausea (2%) and pyrexia (2%). No grade 5 treatment-related AEs occurred within 30 days of the final dose of study therapy. One patient died from study drug toxicity 38 days after the last cycle of nivolumab plus AVD. Grade 3/4 immune-mediated AEs included hepatitis (4%) and elevated transaminase (6%); all these cases resolved.

At the end of study therapy, the ORR was 84% according to both investigator and independent review and included CR rates of 80% vs 67%, respectively (Figure 9). Among the 46 evaluable patients, the ORR was 93%, and included CR rates of 74% by independent review vs 89% by investigator review. Modified 9-month PFS as assessed by independent review was 94% (95% CI, 82%-98%).

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# Highlights in Lymphoma From the 2017 American Society of Hematology Meeting: Commentary

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he 2017 American Society of Hematology (ASH) meeting was marked by a presentation at the plenary session of data from the ECHELON-1 study (Phase 3 Frontline Therapy Trial in Patients With Advanced Classical Hodgkin Lymphoma), which compared brentuximab vedotin and doxorubicin, vinblastine, and dacarbazine (AVD) vs doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) for advanced-stage Hodgkin lymphoma. There were a number of other studies that focused on the brentuximab vedotin/AVD program. Data were also presented for treatments such as nivolumab; ofatumumab, bendamustine, and bortezomib; pembrolizumab combined with rituximab; pralatrexate with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); and duvelisib in combination with romidepsin or bortezomib.

## Hodgkin Lymphoma

### Brentuximab Vedotin

Dr Joseph Connors presented results from the randomized, phase 3 ECHE-LON-1 study of brentuximab vedotin plus AVD vs ABVD in patients with advanced-stage Hodgkin lymphoma.1 Results of this trial were simultaneously published in the New England Journal of Medicine.<sup>2</sup> There are approximately 66,000 cases of Hodgkin lymphoma worldwide. Approximately 40% of these patients have advanced-stage Hodgkin lymphoma. (The most common presentation is that of unfavorable early-stage Hodgkin lymphoma.) In the United States, for decades the standard treatment of advanced-stage Hodgkin lymphoma has been ABVD chemotherapy. From 70% to 75% of patients are cured with this approach. The ECHELON-1 study aimed to improve upon these results by replacing bleomycin in the ABVD regimen with brentuximab vedotin. Brentuximab vedotin has been approved in various settings for Hodgkin lymphoma management, including for palliation, as maintenance therapy after an autologous stem cell transplant (per the AETHERA study [A Phase 3 Study of Brentuximab Vedotin (SGN-35) in Patients at High Risk of Residual Hodgkin Lymphoma Following Stem Cell Transplant]<sup>3</sup>), and as second salvage chemotherapy prior to autologous stem cell transplant. ECH-ELON-1 is a registration trial that enrolled patients with advanced-stage Hodgkin lymphoma from more than 200 sites worldwide. Patients were randomly assigned 1-to-1 to either 6 cycles of ABVD or 6 cycles of brentuximab vedotin plus AVD. The dose of brentuximab vedotin was 1.2 mg/kg. An interim positron emission tomography (PET) scan was performed after

cycle 2. The study used a new primary endpoint called modified progressionfree survival (PFS), which was defined as the time to progression, death from any cause, or a position emission tomography scan showing a Deauville score of 3, 4, or 5 after completion of frontline therapy followed by additional anticancer therapy, whether or not there was a defined histologic progression. In my view, the modified PFS endpoint is a favorable one for a randomized study in lymphoma. However, this endpoint makes the results somewhat difficult to interpret because it is common to use consolidation radiotherapy for bulky disease in advanced-stage Hodgkin lymphoma. If used, this would be considered an event based upon this endpoint.

There were 664 patients in the brentuximab vedotin plus AVD arm and 670 patients in the ABVD arm. There was a male predominance. Most of the patients were young (<45 years), and most were treated in Europe. Two-thirds of the patients had stage IV disease. Only 25% of the patients had an International Prognostic Score of 4 to 7.

Use of brentuximab vedotin was associated with a 5% improvement in modified PFS. Progressive disease was seen in 90 patients treated with brentuximab vedotin plus AVD vs 102 patients treated with ABVD. There were 18 deaths in the brentuximab vedotin plus AVD arm and 22 deaths in the ABVD arm. The modified progression analysis showed that an additional 13 events were caused by either additional chemotherapy or radiotherapy.<sup>2</sup> There was no difference in overall survival. The Forrest plot analysis showed that brentuximab vedotin plus AVD was superior in almost all subgroups. Interestingly, there was no difference between the arms among patients with stage 3 disease without extranodal involvement. which has implications for treatment. A somewhat surprising finding was that the outcome for the 186 patients

older than 59 years was excellent in both arms.

As expected, the brentuximab vedotin plus AVD arm was more toxic than the ABVD arm in terms of neuropathy, infections, and febrile neutropenia. Unfortunately, primary prophylaxis with granulocyte colonystimulating factor (G-CSF) was not mandatory in all treatment centers worldwide. In the United States, where G-CSF was used routinely, there were fewer infectious complications. Interestingly, in the United States, there was also an improvement in modified PFS compared with that seen in other countries, by nearly 10%.

ECHELON-1 is the first study, outside of the BEACOPP programs,<sup>4</sup> to show that ABVD was inferior to another treatment, based upon the endpoint of modified PFS. The study did not, however, provide a significant amount of information on subset analyses. Based on both the published article and the presentation at ASH, I would recommend that patients with stage 4 disease receive brentuximab vedotin plus AVD, if this regimen is approved. For patients with stage 3 disease, I see no reason for this treatment program to be used, pending other analyses.

There were several other presentations on Hodgkin lymphoma that may have an impact on patient management. Dr Andrew Evens presented results that support the use of brentuximab vedotin plus AVD in elderly patients.<sup>5</sup> This study evaluated sequential brentuximab vedotin plus AVD chemotherapy followed by posttreatment brentuximab vedotin in elderly patients with Hodgkin lymphoma. These results were previously presented in a shorter format.<sup>6</sup> The presentation by Dr Evens provided the final data. This study has the best results I have seen among patients with Hodgkin lymphoma who are ages 60 to 80 years and fit for chemotherapy. In fact, the results are no different from those seen with brentuximab vedotin plus AVD

in the ECHELON-1 study, and the sequential regimen is probably easier to tolerate than concomitant brentuximab vedotin plus AVD. My institution participated in this study, and it is a long treatment program, lasting almost 9 months. An interesting result is that after 2 cycles of brentuximab vedotin, given initially as first treatment, nearly all patients responded to therapy. There were several complete responses. Posttreatment brentuximab vedotin was also fairly well-tolerated. Once this study is published, I expect that this regimen will become the standard treatment program for elderly patients with Hodgkin lymphoma. In this older patient population, the sequential treatment was better tolerated than concomitant brentuximab vedotin plus AVD.

Dr Anita Kumar presented the results of a study evaluating brentuximab vedotin plus AVD and 20 Gy of radiotherapy among patients with unfavorable early-stage Hodgkin lymphoma.7 Results from patients in the first cohort, who were treated with 30 Gy of radiotherapy, were previously published in Blood.8 Nearly all of the patients in the first cohort did well and are currently alive and free of disease. For the second cohort, the dose of radiotherapy was reduced by 10 Gy. The presentation by Dr Kumar was well-received. All 29 patients in this cohort were progression-free. The follow-up for a third cohort is now nearly complete; these patients are being treated with residual site radiation therapy, which radiates only PET-negative residual lymph node sites. I anticipate that these data will be presented at the International Symposium on Hodgkin Lymphoma in Cologne, Germany, in October 2018

Another brentuximab vedotin plus AVD program was presented by the Lymphoma Study Association (LYSA).<sup>9</sup> The study aimed to determine if PET 2 could be a reasonable endpoint in patients with early-stage

Hodgkin lymphoma and be used in random assignment trials. It was a fairly large study, enrolling 170 patients. Nearly 85% of the patients had a PET-2 negative response, which was the primary endpoint. One can imagine using this endpoint for potential PET-adapted therapy. It is unclear if patients do in fact require 12 doses of brentuximab vedotin plus AVD to achieve an 80% to 85% 3-year PFS. If the PET scan is negative after 2 cycles, it might be feasible to administer 4 doses of brentuximab vedotin plus AVD. If the PET scan is negative, then brentuximab vedotin may no longer be needed.

Dr Alex Herrera presented final results of a trial evaluating brentuximab vedotin in combination with nivolumab as salvage chemotherapy for patients with relapsed or refractory Hodgkin lymphoma.<sup>10</sup> Previous results were presented earlier,11 and the final results were also published in Blood.12 Of note, more than 60% of the patients in this study had a PET-negative complete response prior to stem cell transplant. The treatment program was well-tolerated, with minimal immunerelated adverse events. This treatment does not have a superior outcome compared with standard multiagent, platinum-based salvage chemotherapy, but it is given on an outpatient basis and is better tolerated. This regimen will likely be another option for this patient population.

Dr Robert Chen presented results from a phase 2 study of brentuximab vedotin plus ibrutinib in patients with relapsed or refractory Hodgkin lymphoma.<sup>13</sup> Previous therapies included ABVD in 94% and brentuximab vedotin in 25%. The overall response rate was 75%, and the complete response rate was 37%. It was unclear if this combination is better than brentuximab vedotin alone. The combination was well-tolerated. Some of the patients had previously received brentuximab vedotin.

#### Nivolumab

Two studies of nivolumab in Hodgkin lymphoma management were notable. The CheckMate 205 study evaluated AVD plus nivolumab in untreated, advanced-stage patients (a similar population to that of ECHELON-11).14 The treatment program was well-tolerated. Nearly all patients had evidence of improvement at the end of therapy, and it appeared that the majority were in remission. It should be mentioned that this study used PET imaging, which is difficult to interpret in patients receiving checkpoint inhibitors because of the high false-positive rate. I recommend use of computed tomography as opposed to PET imaging in this setting.

Dr Jonathan Cohen presented an interesting study.<sup>15</sup> Nivolumab was administered to patients after disease progression, as confirmed by imaging studies. Several patients had evidence of clinical benefit for 6 to 12 months, which implies that when fluorodeoxyglucose PET is used to determine response evaluation, it may be difficult to determine when treatment with a checkpoint inhibitor, either nivolumab or pembrolizumab, should be stopped. In my opinion, when using a checkpoint inhibitor for palliation, computed tomography should be used for initial evaluation. When there is evidence of tumor shrinkage, it is unclear if any further imaging studies are necessary. Treatment should continue unless there is obvious clinical progression.

## Non-Hodgkin Lymphoma

## Brentuximab Vedotin

Dr Jakub Svoboda presented results from a study evaluating the combination of brentuximab vedotin with rituximab plus cyclophosphamide, doxorubicin, and prednisone (R-CHP) chemotherapy as frontline treatment of patients with primary mediastinal large B-cell lymphoma, diffuse large B-cell lymphoma, and gray-zone lymphoma.<sup>16</sup> All patients were CD30positive; brentuximab vedotin binds to CD30. In this open-label study, brentuximab vedotin at a standard dose was substituted for vincristine. Growth factor support was administered to all patients. The study enrolled 31 patients at 3 centers. In general, the treatment program was well-tolerated. Sensory neuropathy was seen in 45% of patients, and motor neuropathy occurred in 10% of patients. The overall response rate in patients who underwent end-of-treatment evaluation was 100%. At a median follow-up of 17 months, the median PFS and overall survival had not been reached. This treatment program warrants further investigation in these patient populations.

## Ofatumumab, Bendamustine, and Bortezomib

A randomized, phase 2 study from the Alliance for Clinical Trials in Oncology compared ofatumumab/bendamustine vs ofatumumab/bendamustine/bortezomib followed by maintenance therapy in untreated patients with high-risk follicular lymphoma.<sup>17</sup> The results were disappointing. Unfortunately, there were no differences in the rates of complete response or overall response between the 2 treatment programs. Compared with bendamustine and rituximab, these more-complicated regimens offered no benefit.

### Pembrolizumab and Rituximab

Dr Loretta Nastoupil presented data for pembrolizumab combined with rituximab in relapsed follicular lymphoma.<sup>18</sup> In general, this was a favorable patient population. All 30 patients were sensitive to rituximab. The treatment regimen consisted of 4 weekly doses of rituximab, plus pembrolizumab given every 3 weeks for a year. After treatment, approximately 50% of the patients were still in a minimal disease state. However, there was a significant amount of immunerelated adverse events with the combination, higher than that seen with single-agent rituximab in the same setting. Of note, high levels of CD8positive T-cell effector scores, based on NanoString analysis, correlated with a complete response. Checkpoint inhibitors and rituximab, with or without other agents, are a platform in follicular lymphoma.

### Pralatrexate and CHOP

Dr Andrei Shustov presented results from a phase 1 dose-escalation study evaluating pralatrexate in combination with CHOP in previously untreated patients with peripheral T-cell lymphoma.<sup>19</sup> There is no standard upfront therapy for peripheral T-cell lymphoma, and many experts recommend investigational therapy. This standard, 3-plus-3, dose-escalation study evaluated pralatrexate administered at various doses along with standard CHOP chemotherapy. Antimicrobial prophylaxis, growth-factor support, and leucovorin rescue therapy were administered. Among the 31 patients enrolled in the study, 29 were evaluable for response. The maximum tolerated dose was not reached, and pralatrexate at 30 mg/m<sup>2</sup> is the dose that will be used in the phase 2 study. The most common adverse events were fatigue and constipation. Approximately 10% of patients had grade 3/4 mucositis. The overall response rate was 90%, and the complete response rate was 66%, which is encouraging. I anticipate that these data will lead to a randomized study.

## Duvelisib With Romidepsin or Bortezomib

A multicenter group reported on the results of a parallel, phase 1 study of duvelisib in combination with romidepsin or bortezomib in patients with relapsed or refractory T-cell lymphoma.<sup>20</sup> There is no standard of care in this patient population. Approximately 30 patients were treated during the study. There were 15 patients evaluable for response in the romidepsin/duvelisib arm and 17 patients in the bortezomib/duvelisib arm. The overall response rates were 50% in the duvelisib/romidepsin arm and 35% in the bortezomib/duvelisib arm. Unfortunately, there was more toxicity in the bortezomib/duvelisib arm. The romidepsin/duvelisib arm will move forward into a phase 2 trial. Both treatment programs, however, are encouraging in the relapsed and refractory setting.

#### Disclosure

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