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A SPECIAL MEETING REVIEW EDITION

Highlights in Lymphoma From the 2018 American Society of Clinical Oncology Annual Meeting

A Review of Selected Presentations From the 2018 American Society of Clinical Oncology Annual Meeting • June 1-5, 2018 • Chicago, Illinois

Special Reporting on:

- Brentuximab Vedotin Plus Chemotherapy in Patients With Newly Diagnosed Advanced-Stage Hodgkin Lymphoma: North American Results
- Randomized Phase III Study Comparing an Early PET-Driven Treatment De-Escalation to a Not PET-Monitored Strategy in Patients With Advanced-Stages Hodgkin Lymphoma: Final Analysis of the AHL2011 LYSA Study
- Improving Outcomes With Brentuximab Vedotin Plus Chemotherapy in Patients With Newly Diagnosed Advanced-Stage Hodgkin Lymphoma
- Activity and Tolerability of the First-in-Class Anti-CD47 Antibody Hu5F9-G4 With Rituximab Tolerated in Relapsed/Refractory Non-Hodgkin Lymphoma: Initial Phase 1b/2 Results
- Brentuximab Vedotin With Chemotherapy for Stage III or IV Hodgkin Lymphoma: Impact of Cycle 2 PET Result on Modified Progression-Free Survival
- Durability of Response in ZUMA-1, the Pivotal Phase 2 Study of Axicabtagene Ciloleucel in Patients With Refractory Large B-Cell Lymphoma
- Long-Term Follow-Up of Brentuximab Vedotin ± Dacarbazine as First-Line Therapy in Elderly Patients With Hodgkin Lymphoma
- Cost-Effectiveness Analysis of Brentuximab Vedotin With Chemotherapy in Newly Diagnosed Stage III/IV Hodgkin Lymphoma

PLUS Meeting Abstract Summaries

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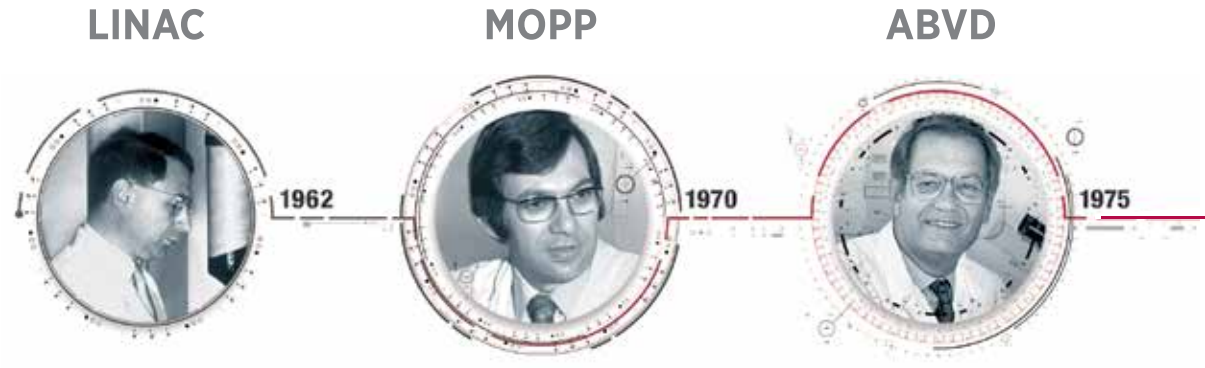
ADCETRIS® (brentuximab vedotin) + AVD

THE FIRST FDA-APPROVED FRONTLINE REGIMEN IN OVER 40 YEARS

for Stage III/IV classical Hodgkin lymphoma (cHL)



KAPLAN

The introduction of the linear accelerator revolutionizes radiation therapy in cHL[1]

DEVITA

The first multi-agent chemotherapy regimen for cHL proves new possibilities for outcomes[2]

BONADONNA

Using the latest advances in chemotherapy, the ABVD regimen further improves outcomes in cHL[3]

Indication

ADCETRIS® (brentuximab vedotin) is indicated for adult patients with previously untreated Stage III/IV classical Hodgkin lymphoma (cHL) in combination with chemotherapy.

Important Safety Information

BOXED WARNING

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML): JC virus infection resulting in PML and death can occur in ADCETRIS-treated patients.

Contraindication

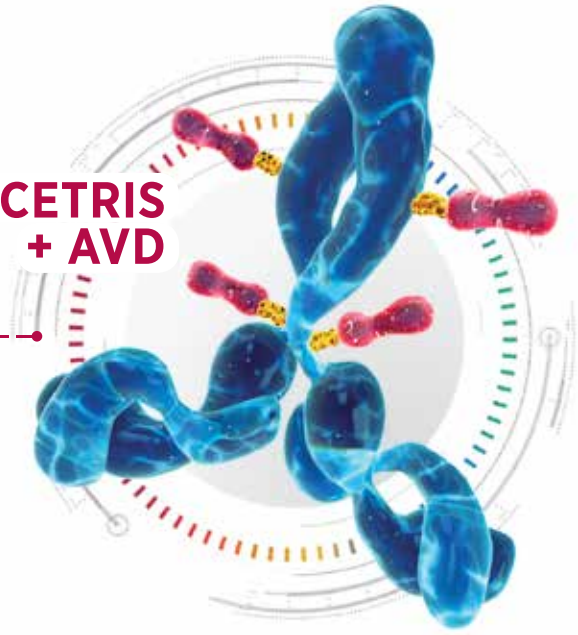
ADCETRIS concomitant with bleomycin due to pulmonary toxicity (e.g., interstitial infiltration and/or inflammation).

Warnings and Precautions

- Peripheral neuropathy (PN): ADCETRIS causes PN that is predominantly sensory. Cases of motor PN have also been reported. ADCETRIS-induced PN is cumulative. Monitor for symptoms such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Institute dose modifications accordingly.

SUPERIOR EFFICACY vs ABVD

with no exposure to bleomycin



23% reduction in risk of progression, death, or receipt of additional anticancer therapy

Modified PFS per IRF: HR: 0.77 (95% CI: 0.60, 0.98); $P = 0.035$[4]

Explore clinical data at

adcetrispro.com

ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; AVD = doxorubicin, vinblastine, dacarbazine; CI = confidence interval; HR = hazard ratio; IRF = independent review facility; LINAC = linear accelerator; MOPP = mechlorethamine, vincristine, procarbazine, prednisone; PFS = progression-free survival; OS = overall survival.

GENERATION A : **ADCETRIS + AVD**

ECHELON-1 TRIAL DESIGN: A randomized, open-label, multicenter trial assessing the efficacy and safety of ADCETRIS plus AVD [A+AVD] vs ABVD in 1334 adult patients with newly diagnosed Stage III/IV cHL. 664 patients were randomized to receive 1.2 mg/kg of ADCETRIS administered as an IV infusion over 30 minutes every 2 weeks for up to 12 doses + AVD, and 670 patients were randomized to 12 doses of ABVD. The primary endpoint was modified PFS per IRF. The key secondary endpoint was OS.[4,5]

Interim OS analysis

OS data are immature; an interim OS analysis did not demonstrate a significant difference between treatment arms*[4]

Most common adverse reactions (≥20%) in patients treated with A+AVD

Anemia (98%); neutropenia (91%); peripheral sensory neuropathy (65%); constipation (42%); vomiting (33%); diarrhea (27%); pyrexia (27%); decreased weight (22%); stomatitis (21%); abdominal pain (21%)[4]

*At the time of modified PFS analysis.

Please see additional Important Safety Information and Brief Summary of Prescribing Information, including BOXED WARNING, on the following pages. Full Prescribing Information available at adcetrispro.com

CD30-DIRECTED
ADCETRIS®
brentuximab vedotin | for injection

Important Safety Information (cont'd)

- Anaphylaxis and infusion reactions: Infusion-related 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: Fatal and serious cases of febrile neutropenia have been reported with ADCETRIS. Prolonged (≥1 week) severe neutropenia and Grade 3 or 4 thrombocytopenia or anemia can occur with ADCETRIS.

  Administer G-CSF primary prophylaxis starting with Cycle 1 for previously untreated patients who receive ADCETRIS in combination with chemotherapy for Stage III/IV cHL.

  Monitor complete blood counts prior to each ADCETRIS dose. 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 doses.
- Serious infections and opportunistic infections: Infections such as pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes) have been reported in ADCETRIS-treated 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: Fatal and serious cases have occurred in ADCETRIS-treated 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: Fatal cases of JC virus infection resulting in PML have 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. In addition to ADCETRIS therapy, other possible contributory factors include prior therapies and underlying disease that may cause immunosuppression. Consider PML diagnosis 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: Fatal and serious events of noninfectious pulmonary toxicity, including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome 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: Fatal and serious cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with ADCETRIS. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.
- Gastrointestinal (GI) complications: Fatal and serious cases of acute pancreatitis have been reported. Other fatal and serious 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.
- 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.

Most Common (≥20%) Adverse Reactions

Neutropenia, anemia, peripheral sensory neuropathy, nausea, fatigue, constipation, diarrhea, vomiting, and pyrexia.

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. Kaplan HS. The radical radiotherapy of regionally localized Hodgkin's disease. *Radiology*. 1962;78:553-561. **2.** DeVita VT Jr, Serpick AA, Carbone PP. Combination chemotherapy in the treatment of advanced Hodgkin's disease. *Ann Intern Med*. 1970;73:881-895. **3.** Bonadonna G, Zucali R, Monfardini S, De Lena M, Uslenghi C. Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. *Cancer*. 1975;36(1):252-259. **4.** ADCETRIS [Prescribing Information], Bothell, WA: Seattle Genetics, Inc. March 2018. **5.** Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. *N Engl J Med*. 2018;378:331-344.

SeattleGenetics®

CD30-DIRECTED
ADCETRIS®
brentuximab vedotin | for injection

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

Initial U.S. approval: 2011

Brief Summary: see package insert for full prescribing information

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

JC virus infection resulting in PML and death can occur in patients receiving ADCETRIS.

1 INDICATIONS AND USAGE

ADCETRIS is a CD30-directed antibody-drug conjugate indicated for adult patients with previously untreated Stage III/IV classical Hodgkin lymphoma (cHL), in combination with chemotherapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

For dosing instructions of combination agents administered with ADCETRIS, see the manufacturer's prescribing information.

Administer ADCETRIS as an intravenous infusion over 30 minutes every 2 weeks until a maximum of 12 doses, disease progression, or unacceptable toxicity.

The recommended dose is 1.2 mg/kg up to a maximum of 120 mg in combination with chemotherapy. Reduce the dose in patients with mild hepatic impairment (Child-Pugh A) to 0.9 mg/kg up to a maximum of 90 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 Recommended Prophylactic Medications

In patients with previously untreated Stage III/IV cHL who are treated with ADCETRIS +AVD, administer G-CSF beginning with Cycle 1.

2.3 Dose Modification

Peripheral Neuropathy: For Grade 2 peripheral neuropathy, reduce dose to 0.9 mg/kg up to a maximum of 90 mg every 2 weeks. For Grade 3 peripheral neuropathy, hold dosing until improvement to Grade 2 or lower. Restart at 0.9 mg/kg, up to a maximum of 90 mg, every 2 weeks. Consider modifying the dose of other neurotoxic chemotherapy agents. For Grade 4 peripheral neuropathy, discontinue dosing. 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, administer G-CSF prophylaxis for subsequent cycles for patients not receiving primary G-CSF prophylaxis.

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 a study of ADCETRIS as combination therapy (Study 5, ECHELON-1), 67% of patients treated with ADCETRIS+AVD experienced any grade of neuropathy. The median time to onset of any grade was 8 weeks (range, 0–29), of Grade 2 was 14 weeks (range, 0–28), and of Grade 3 was 16 weeks (range, 1–29). The median time from onset to resolution or improvement of any grade was 10 weeks (range, 0–139), of Grade 2 was 12 weeks (range, 0–123), and of Grade 3 was 17 weeks (range, 0–139). Of these patients, 43% had complete resolution, 24% had partial improvement (a decrease in severity by one or more grade from worst grade) and 33% had no improvement at the time of their last evaluation. Of the patients with residual neuropathy at the time of their last evaluation (57%), patients reported Grade 1 (36%), Grade 2 (16%), Grade 3 (4%), or Grade 4 (1 patient) neuropathy. Median time of overall study follow-up was 84.3 weeks (range, 0–194).

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

Fatal and serious cases of febrile neutropenia have been reported with ADCETRIS. Prolonged (≥1 week) severe neutropenia and Grade 3 or Grade 4 thrombocytopenia or anemia can occur with ADCETRIS.

Start primary prophylaxis with G-CSF beginning with Cycle 1 for previously untreated patients who receive ADCETRIS in combination with chemotherapy for Stage III/IV cHL. 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 ≥Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. Due to higher MMAE exposure, ≥Grade 3 adverse reactions may be more frequent in patients with severe renal impairment compared to patients with normal renal function. Avoid the use of ADCETRIS in patients with severe renal impairment (CrCL <30 mL/min).

5.7 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 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

Fatal and serious cases of hepatotoxicity 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

Fatal cases of JC virus infection resulting in PML have 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

Fatal and serious events of noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome (ARDS), 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

Fatal and serious cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with ADCETRIS. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.

5.12 Gastrointestinal Complications

Fatal and serious events of acute pancreatitis have 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. Advise a pregnant woman 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.

The data below reflect exposure to ADCETRIS in 931 patients with cHL including 662 patients who received ADCETRIS in combination with chemotherapy in a randomized controlled trial, and 269 who received ADCETRIS as monotherapy (167 in a randomized

controlled trial and 102 in a single arm trial). Data summarizing ADCETRIS exposure are also provided for 58 patients from a single arm evaluation of ADCETRIS monotherapy in systemic anaplastic large cell lymphoma (sALCL) and 66 patients from a randomized controlled evaluation of ADCETRIS monotherapy in primary cutaneous anaplastic large cell lymphoma (pcALCL) and CD30-expressing mycosis fungoides (MF). ADCETRIS was administered intravenously at a dose of either 1.2 mg/kg every 2 weeks (in combination with chemotherapy) or 1.8 mg/kg every 3 weeks (as monotherapy).

The most common adverse reactions (≥20%) were neutropenia, anemia, peripheral sensory neuropathy, nausea, fatigue, constipation, diarrhea, vomiting, and pyrexia.

Previously Untreated Stage III/IV cHL (Study 5: ECHELON-1)

ADCETRIS in combination with chemotherapy was evaluated for the treatment of previously untreated patients with Stage III/IV cHL in a randomized, open-label, multicenter clinical trial of 1334 patients. Patients were randomized to receive up to 6 cycles of ADCETRIS+AVD or ABVD on Days 1 and 15 of each 28-day cycle. The recommended starting dose of ADCETRIS was 1.2 mg/kg intravenously over 30 minutes, administered approximately 1 hour after completion of AVD therapy. A total of 1321 patients received at least one dose of study treatment (662 ADCETRIS+AVD, 659 ABVD). The median number of treatment cycles in each study arm was 6 (range, 1–6); 76% of patients on the ADCETRIS + AVD arm received 12 doses of ADCETRIS.

After 75% of patients had started study treatment, the use of prophylactic G-CSF was recommended with the initiation of treatment for all ADCETRIS+AVD-treated patients, based on the observed rates of neutropenia and febrile neutropenia. Among 579 patients on the ADCETRIS+AVD arm who did not receive G-CSF primary prophylaxis beginning with Cycle 1, 96% experienced neutropenia (21% with Grade 3; 67% with Grade 4), and 21% had febrile neutropenia (14% with Grade 3; 6% with Grade 4). Among 83 patients on the ADCETRIS+AVD arm who received G-CSF primary prophylaxis beginning with Cycle 1, 61% experienced neutropenia (13% with Grade 3; 27% with Grade 4), and 11% experienced febrile neutropenia (8% with Grade 3; 2% with Grade 4).

Serious adverse reactions, regardless of causality, were reported in 43% of ADCETRIS+AVD-treated patients and 27% of ABVD-treated patients. The most common serious adverse reactions in ADCETRIS+AVD-treated patients were febrile neutropenia (17%), pyrexia (7%), neutropenia and pneumonia (3% each).

Adverse reactions that led to dose delays of one or more drugs in more than 5% of ADCETRIS+AVD-treated patients were neutropenia (21%) and febrile neutropenia (8%). Adverse reactions led to treatment discontinuation of one or more drugs in 13% of ADCETRIS+AVD-treated patients. Seven percent of patients treated with ADCETRIS+AVD discontinued due to peripheral neuropathy.

There were 9 on-study deaths among ADCETRIS+AVD-treated patients; 7 were associated with neutropenia, and none of these patients had received G-CSF prior to developing neutropenia.

Table 4: Adverse Reactions Reported in ≥10% of ADCETRIS+AVD-treated Patients in Previously Untreated Stage III/IV cHL (Study 5: ECHELON-1)

	ADCETRIS+AVD Total N = 662 % of patients			ABVD Total N = 659 % of patients		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders						
Anemia*	98	11	<1	92	6	<1
Neutropenia*	91	20	62	89	31	42
Febrile neutropenia*	19	13	6	8	6	2
Gastrointestinal disorders						
Constipation	42	2	-	37	<1	<1
Vomiting	33	3	-	28	1	-
Diarrhea	27	3	<1	18	<1	-
Stomatitis	21	2	-	16	<1	-
Abdominal pain	21	3	-	10	<1	-
Nervous system disorders						
Peripheral sensory neuropathy	65	10	<1	41	2	-
Peripheral motor neuropathy	11	2	-	4	<1	-
General disorders and administration site conditions						
Pyrexia	27	3	<1	22	2	-
Musculoskeletal and connective tissue disorders						
Bone pain	19	<1	-	10	<1	-
Back pain	13	<1	-	7	-	-
Skin and subcutaneous tissue disorders						
Rashes, eruptions and exanthems†	13	<1	<1	8	<1	-
Respiratory, thoracic and mediastinal disorders						
Dyspnea	12	1	-	19	2	-
Investigations						
Decreased weight	22	<1	-	6	<1	-
Increased alanine aminotransferase	10	3	-	4	<1	-
Metabolism and nutrition disorders						
Decreased appetite	18	<1	-	12	<1	-
Psychiatric disorders						
Insomnia	19	<1	-	12	<1	-

*Derived from laboratory values and adverse reaction data; data are included for clinical relevance irrespective of rate between arms.

†Grouped term includes rash maculo-papular, rash macular, rash, rash papular, rash generalized, and rash vesicular.

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

Events were graded using the NCI CTCAE Version 4.03. Events listed are those having a ≥5% difference in rate between treatment arms.

Additional Important Adverse Reactions

Infusion reactions

In a study of ADCETRIS as combination therapy (Study 5, ECHELON-1), infusion-related reactions were reported in 57 patients (9%) in the ADCETRIS+AVD-treated arm. Grade 3 events were reported in 3 of the 57 patients treated with ADCETRIS+AVD who experienced infusion-related reactions. The most common adverse reaction (≥2%) associated with infusion-related reactions was nausea (2%).

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. 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.

In a study of ADCETRIS as combination therapy (Study 5, ECHELON-1), non-infectious pulmonary toxicity events were reported in 12 patients (2%) in the ADCETRIS+AVD arm. These events included lung infiltration (6 patients) and pneumonitis (6 patients), or interstitial lung disease (1 patient).

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 to ADCETRIS in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Patients with cHL and sALCL in Studies 1 and 2 were tested for antibodies to brentuximab vedotin every 3 weeks using a sensitive electrochemiluminescence immunoassay. Approximately 7% of patients in these trials developed persistently positive antibodies (positive test at more than 2 time points) and 30% developed transiently positive antibodies (positive at 1 or 2 post-baseline time points). 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.

8 USE IN SPECIFIC POPULATIONS

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]*. The available data from case reports on ADCETRIS use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. Advise a pregnant woman of the potential risk to a fetus.

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 ADCETRIS.

8.4 Pediatric Use

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

8.5 Geriatric Use

In the clinical trial of ADCETRIS in combination with chemotherapy for patients with previously untreated Stage III/IV cHL, (Study 5: ECHELON-1), 9% of ADCETRIS+AVD-treated patients were aged 65 or older. Older age was a risk factor for febrile neutropenia, occurring in 39% of patients aged 65 or older vs. 17% of patients less than age 65, who received ADCETRIS+AVD. The ECHELON-1 trial did not contain sufficient information on patients aged 65 and over to determine whether they respond differently from younger patients.

Other 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.

8.7 Hepatic Impairment

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.

10 OVERDOSAGE

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

17 PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

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

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.

Please see full Prescribing Information, including BOXED WARNING, at adcetrispro.com

SeattleGenetics®

USP-BVP-2018-0119(1)

Brentuximab Vedotin Plus Chemotherapy in Patients With Newly Diagnosed Advanced-Stage Hodgkin Lymphoma: North American Results

Prespecified analyses were conducted to assess safety and efficacy results in North American treatment centers that participated in the ECHELON-1 trial (Phase 3 Frontline Therapy Trial in Patients With Advanced Classical Hodgkin Lymphoma).[1] Eighty-five sites in the United States and Canada were included. The primary endpoint of ECHELON-1 was modified progression-free survival (PFS), which included time to progression, death, or noncomplete response based on independent review, plus use of subsequent therapy to treat Hodgkin lymphoma (HL). Overall survival (OS) was the key secondary endpoint. After a median follow-up of 24.6 months, 2-year modified PFS rates were 82.1% with brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (AVD) vs 77.2% with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD; hazard ratio [HR] for an event of progression, death, or modified progression, 0.77; 95% CI, 0.60-0.98; *P*=.04).[2] Based on the trial results, in March 2018, the US Food and Drug Administration (FDA) expanded the indication of brentuximab vedotin (in combination with chemotherapy) to include the treatment of adults with previously untreated stage III/IV classical HL.[3]

Modified PFS as assessed by an independent review facility in North America was a prespecified analysis. Exploratory analyses of the North American subgroup included investigator-determined modified PFS as well as PFS, with PFS defined as the time from randomization to disease progression or death from any cause. PFS and modified PFS were determined by Kaplan-Meier analysis. In North America, 250 patients were randomly assigned to receive brentuximab vedotin plus AVD and 247 to receive ABVD. Patient characteristics were well-balanced between the 2 arms. Patients underwent imaging with computed tomography/position emission tomography (PET).

The median follow-up was approximately 25 months. The modified PFS at 2 years as determined by independent review was 84.3% (95% CI, 78.7%-88.5%) with brentuximab vedotin plus AVD vs 73.7% (95% CI, 67.3%-79.1%) with ABVD (HR, 0.596; 95% CI, 0.395-0.899; *P*=.012; Figure 1). The modified PFS as assessed by investigators was 86.4% (95% CI,

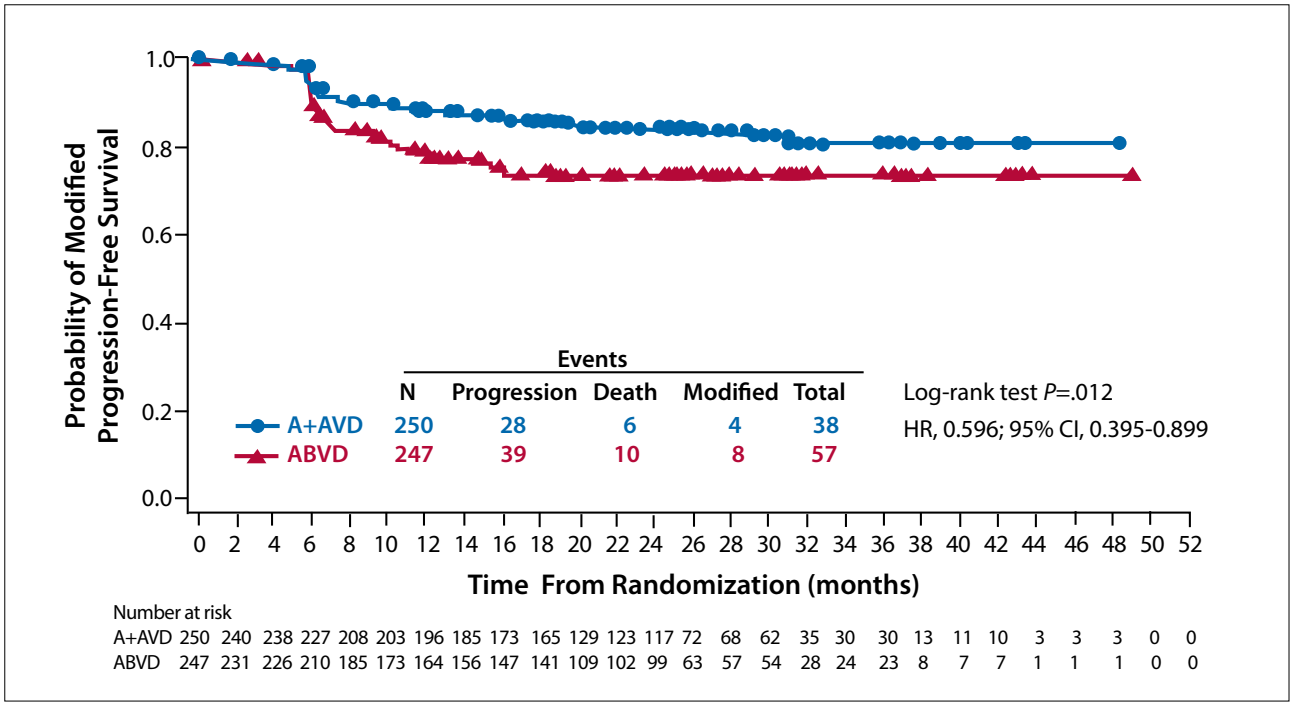


Figure 1. Modified progression-free survival in a study of brentuximab vedotin plus chemotherapy per analysis from an independent review facility. A+AVD, brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; HR, hazard ratio. Adapted from Ramchandren R et al. ASCO abstract 7541. *J Clin Oncol.* 2018;36(15 suppl).[1]

ABSTRACT SUMMARY RELEVANCE: Phase III Randomized Study of Lenalidomide Plus Rituximab Versus Chemotherapy Plus Rituximab, Followed by Rituximab Maintenance, in Patients With Previously Untreated Follicular Lymphoma

The open-label, multicenter, international phase 3 RELEVANCE trial (Combined Rituximab and Lenalidomide Treatment for Untreated Patients With Follicular Lymphoma) compared lenalidomide plus rituximab vs rituximab plus chemotherapy, followed by rituximab maintenance, in patients with newly diagnosed, advanced follicular lymphoma (Abstract 7500). The study included 1030 patients, whose median age was 59 years (range, 23-89 years). Forty percent had bulky disease, and nearly half had high-risk disease. The co–primary endpoint of CR/unconfirmed CR at 120 weeks showed no significant difference between the 2 treatment arms (48% for lenalidomide plus rituximab vs 53% with immunochemotherapy; *P*=.13). The 3-year duration of response was 77% for lenalidomide plus rituximab vs 74% for immunochemotherapy. After a median follow-up of 37.9 months, interim 3-year PFS by independent review was 77% (95% CI, 72%-80%) with lenalidomide plus rituximab vs 78% with immunochemotherapy (HR, 1.10; 95% CI, 0.85-1.43; *P*=.48). Prespecified subgroup analyses and OS analysis also yielded no significant differences between the 2 arms. However, the 2 treatments were associated with different safety profiles. Patients in the immunochemotherapy arm were more likely to experience grade 3/4 neutropenia (50% vs 32%), grade 4 neutropenia (31% vs 8%), and febrile neutropenia (7% vs 2%). They were also more likely to receive growth factors (68% vs 23%).

81.3%-90.2%) with brentuximab vedotin plus AVD vs 73.6% (95% CI, 67.2%-78.9%) in the standard treatment arm (HR, 0.516; 95% CI, 0.339-0.786; *P*=.002). The investigator-assessed standard PFS at 2 years was 88.1% (95% CI, 83.1%-91.7%) vs 76.4% (95% CI, 70.1%-81.5%), respectively (HR, 0.500; 95% CI, 0.318-0.786; *P*=.002). Brentuximab vedotin plus AVD showed a benefit or a trend toward a benefit in most subgroups, including patients with baseline stage IV disease (HR, 0.554; 95% CI, 0.327-0.937), a high International Prognostic Score (HR, 0.396; 95% CI, 0.199-0.789), and B symptoms (HR, 0.664; 95% CI, 0.391-1.127).

Response rates were consistently superior with brentuximab vedotin plus AVD. The independent review yielded PET-negativity rates after treatment cycle 2 of 88% with brentuximab vedotin plus AVD vs 83% with ABVD, and the proportion of patients with a Deauville score of 2 or less after completion of first-line therapy was 85% vs 76%. The CR rates were 72% vs 67% (based on revised Cheson response criteria[4]). Grade 3 or higher adverse events (AEs) were more common among patients treated with brentuximab vedotin plus AVD (81% vs 67%), as were drug-related AEs of grade 3 or higher (77% vs 56%). AEs led to treatment discontinuation in 15% of the brentuximab vedotin plus AVD arm vs 24% in the ABVD arm. Peripheral neuropathy of any grade was more common in patients treated with brentuximab vedotin plus AVD (80% vs 56%), and included an increase in the rate of grade 3 peripheral neuropathy (17% vs <1%). Rates of pulmonary toxicity were higher in the ABVD arm (10% vs 3% for any grade; 6% vs 2% for grade 3 or higher). Among the 7 deaths in the ABVD arm, 6 were related to pulmonary toxicity. Two patients died in the brentuximab vedotin arm.

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Randomized Phase III Study Comparing an Early PET-Driven Treatment De-Escalation to a Not PET-Monitored Strategy in Patients With Advanced-Stages Hodgkin Lymphoma: Final Analysis of the AHL2011 LYSA Study

Treatment with 6 cycles of escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) can achieve long-term control of HL.[1,2] Compared with ABVD, escalated BEACOPP improves PFS. It does not improve OS, however, and it can be associated with myelodysplastic syndrome/acute myeloid leukemia and infertility. The use of PET imaging to characterize

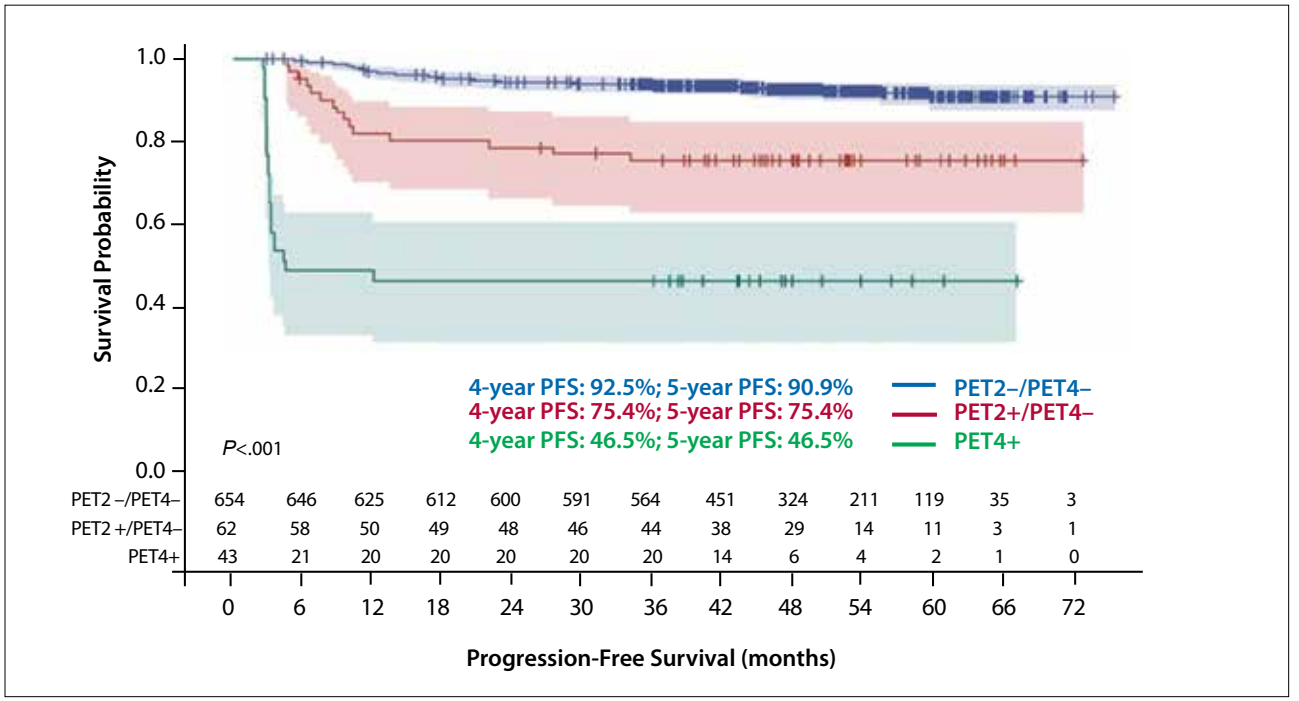

Figure 2. PFS according to PET-driven strategies in a study of escalated BEACOPP. BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; PET2, positron emission tomography imaging performed after treatment cycle 2; PET4, positron emission tomography imaging performed after treatment cycle 4; PFS, progression-free survival. Adapted from Casasnovas O et al. ASCO abstract 7503. *J Clin Oncol.* 2018;36(15 suppl).[3]

early responses could enable de-escalation of treatment after escalated BEACOPP without sacrificing disease control.

The phase 3 AHL2011 LYSA trial (Advanced Hodgkin Lymphoma 2011 Lymphoma Study Association) evaluated whether altering therapy based on PET imaging after 2 or 4 cycles of escalated BEACOPP could improve outcome.[3] Eligible patients were ages 16 to 60 years and had classical HL with high-risk stage IIB or stage III/IV disease. Before the 1:1 randomization, patients were stratified based on their International Prognostic Score and stage. PET imaging was performed after treatment cycles 2 (PET2) and 4 (PET4) in both arms. Patients in the standard treatment arm received 6 cycles of escalated BEACOPP. In the experimental arm, patients received 2 initial cycles of escalated BEACOPP. Patients who had a positive PET2 result continued treatment with escalated BEACOPP, whereas those with a negative result switched to 4 cycles of ABVD. In both arms, patients with a positive PET4 result switched to salvage therapy. The trial used a noninferiority 5-year PFS design that anticipated thresholds of 85% in the standard treatment arm and greater than 75% in the experimental arm (HR, 1.77).

The study enrolled 413 patients in the standard treatment arm and 410 in the experimental arm. The patients' median age was 30 years (range, 16-60 years), and 63% were male. Sixty-eight percent of patients had B symptoms, 88% had stage III/IV disease, and 58% had an International Prognostic Score of 3 or higher. PET2 results were positive in 12% of patients in the standard treatment arm and 13% in the experimental arm. Thus, based on the intention-to-treat analysis, 84% of patients in the experimental arm received 2 cycles of escalated BEACOPP followed by 4 cycles of ABVD. After a median follow-up of 50.4 months, the estimated 5-year PFS was 86.2% in the standard treatment arm vs 85.7% in the experimental arm (HR, 1.084; 95% CI, 0.73-1.59; *P*=.68), thus demonstrating noninferiority. The estimated 5-year OS was also similar for the standard and experimental treatment arms (95.2% vs 96.4%, respectively; HR, 0.936; 95% CI, 0.42-2.05; *P*=.91). PET4 results were positive in 7% of patients in the standard treatment arm vs 4% in the experimental arm. PET results correlated with PFS. The estimated 5-year PFS was 90.9% for patients with negative PET2 and PET4 results vs 75.4% for patients with positive PET2 and negative PET4 results (*P*<.001; Figure 2). The estimated 5-year OS was superior in patients with negative PET results after 2 and 4 cycles of escalated BEACOPP (*P*<.04).

Nearly all patients in both arms experienced at least 1 grade 3/4 AE. Grade 3/4 AEs that occurred at higher

rates in the standard treatment arm vs the experimental arm included anemia (69% vs 28%; *P*<.001), thrombocytopenia (66% vs 40%; *P*<.001), and febrile neutropenia (35% vs 23%; *P*<.001). Serious AEs were also more common in the standard treatment arm (27% vs 17%; *P*<.002), as were treatment-related serious AEs (47% vs 28%; *P*<.001). Treatment discontinuation owing to toxicity was noted in 6.8% of patients in the standard treatment arm vs 1% of those in the experimental arm (*P*<.00001). Secondary primary malignancies were observed in 2.4% vs 1.2% (*P*>.05).

ABSTRACT SUMMARY Acalabrutinib in Patients With Waldenström Macroglobulinemia

Acalabrutinib, a covalent inhibitor of Bruton's tyrosine kinase, was evaluated in a phase 2 trial of patients with Waldenström macroglobulinemia (Abstract 7501). Patients with treatment-naive, relapsed or refractory disease received acalabrutinib at 100 mg twice daily until they developed progressive disease or intolerance. Among the 106 patients, 14 were treatment-naive. After a median follow-up of 27.4 months, 72% of patients remained on therapy. The ORR was 93% (95% CI, 66%-100%) for treatment-naive patients and 93% (95% CI, 86%-98%) for previously treated patients. No CRs were observed. The ORR was consistent across subgroups, including patients who had received 3 or more prior therapies (95.5%) and those ages 65 years and older (93.4%). The median 2-year PFS was 90.0% (95% CI, 47.3%-98.5%) for treatment-naive patients and 81.9% (95% CI, 72.1%-88.5%) for patients with relapsed or refractory disease at baseline. Serious AEs occurred in 43% of treatment-naive patients and in 54% of those who had been previously treated.

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Improving Outcomes With Brentuximab Vedotin Plus Chemotherapy in Patients With Newly Diagnosed Advanced-Stage Hodgkin Lymphoma

The open-label, phase 3 ECHELON-1 trial compared 6 cycles of brentuximab vedotin plus AVD vs ABVD in patients with treatment-naive stage III/IV HL.[1] Neutropenia of any grade occurred in 58% of patients treated with brentuximab vedotin plus AVD vs 45% of those treated with ABVD. Granulocyte-colony stimulating factor (G-CSF) was administered at the investigator's discretion, with formal recommendations made by an independent data monitoring committee for patients treated with brentuximab vedotin plus AVD. Among these patients, administration of G-CSF as primary prophylaxis was associated with lower rates of grade 3 or higher neutropenia (29% vs 70%) and febrile neutropenia (11% vs 21%).

Dr David Straus presented results of exploratory analyses comparing outcomes in patients who received G-CSF primary prophylaxis vs those who did not.[2] Among 662 patients treated with brentuximab vedotin plus AVD, 83 received G-CSF primary prophylaxis. The median time to first use of G-CSF was 0.3 weeks (range, 0.1-0.7 weeks). G-CSF primary prophylaxis was associated with reduced rates of hospitalization (29% vs 38%), neutropenia of grade 3 or higher (29% vs 70%), and febrile neutropenia of any grade (11% vs 21%; Figure 3). Among the 9 deaths in the brentuximab vedotin plus AVD arm, 7 were associated with neutropenia, and none of these patients had received G-CSF primary prophylaxis. Peripheral neuropathy was observed in 57% of patients who received G-CSF primary prophylaxis vs 68% of those who did not. G-CSF prophylaxis reduced delays in the administration of brentuximab vedotin (35% vs 49%) and decreased dosage reductions (20% vs 26%).

Patients treated with G-CSF primary prophylaxis before brentuximab vedotin plus AVD demonstrated a numerically reduced risk for modified PFS events, both in comparison with patients in the same arm who did not receive G-CSF primary prophylaxis (HR, 0.737; 95% CI, 0.396-1.372) and in comparison with patients in the ABVD arm (HR, 0.586; 95% CI, 0.317-1.081). The analysis is limited by the small number of patients who received G-CSF primary prophylaxis.

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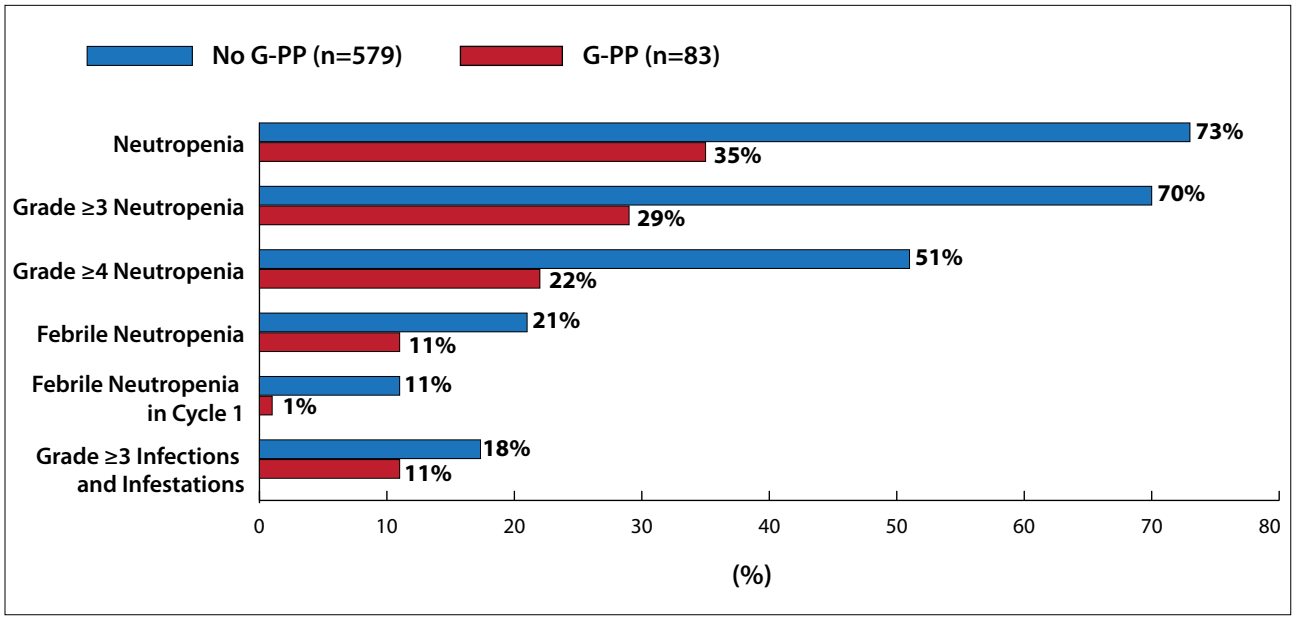

Figure 3. Rates of febrile neutropenia after treatment with brentuximab vedotin plus AVD among patients who did or did not receive primary prophylaxis with granulocyte-colony stimulating factor. AVD, doxorubicin, vinblastine, and dacarbazine; G-PP, primary prophylaxis with granulocyte-colony stimulating factor. Adapted from Straus DJ et al. ASCO abstract 7534. *J Clin Oncol*. 2018;36(15 suppl).[2]

Activity and Tolerability of the First-in-Class Anti-CD47 Antibody Hu5F9-G4 With Rituximab Tolerated in Relapsed/Refractory Non-Hodgkin Lymphoma: Initial Phase 1b/2 Results

Macrophages remove pathogens and unwanted cells by detecting specific cell-surface molecules that induce a signal to commence phagocytosis. Macrophages are also abundant in most tumors and may invoke phagocytosis in response to cancer cells. CD47 is an immunoglobulin-like protein that can interact with SIRPα, a regulatory membrane glycoprotein that is expressed on macrophages.[1] The interaction of CD47 with its receptor on macrophages inhibits phagocytosis; thus, cancer cells may evade phagocytosis through expression of CD47. CD47 expression has been shown to enable a human acute myeloid leukemia cell line to engraft into immunocompromised mice, and increased CD47 expression is associated with a worse prognosis in multiple subtypes of non-Hodgkin lymphoma (NHL), including B-cell NHL.[2] An anti-CD47 monoclonal antibody that enables phagocytosis was evaluated in combination with rituximab for the treatment of mice engrafted with the human NHL cell line. The antibody combination showed synergistic efficacy, eliminating NHL cells in 60% of mice in a disseminated engraftment model and in 86% of mice in a localized engraftment model. Similar results were obtained using xenograft models that were transplanted with primary diffuse large B-cell lymphoma (DLBCL) cells.

A humanized anti-CD47 antibody, Hu5F9-G4 (5F9), binds to CD47 with 8 nM affinity.[3] The antibody induced potent macrophage-mediated phagocytosis of primary human acute myeloid leukemia cells in vitro and eradicated primary human acute myeloid leukemia xenografts in a mouse model. The humanized anti-CD47 antibody also showed synergistic activity with rituximab in a mouse xenograft model of NHL. The synergy is believed to arise from the prophagocytic signals provided by rituximab through its Fc receptor, combined with the ability of 5F9 to intercept CD47.

The combination of 5F9 plus rituximab was evaluated in a phase 1b/2 dose-escalation and expansion study in patients with relapsed or refractory B-cell NHL who required treatment after standard therapies.[4] The trial used a 3 + 3 dose-escalation design. To mitigate anemia and other on-target toxicities, patients received a priming dose of 5F9 at 1 mg/kg, plus higher weekly maintenance doses that ranged from 10 mg/kg to 30 mg/kg. Rituximab was administered at

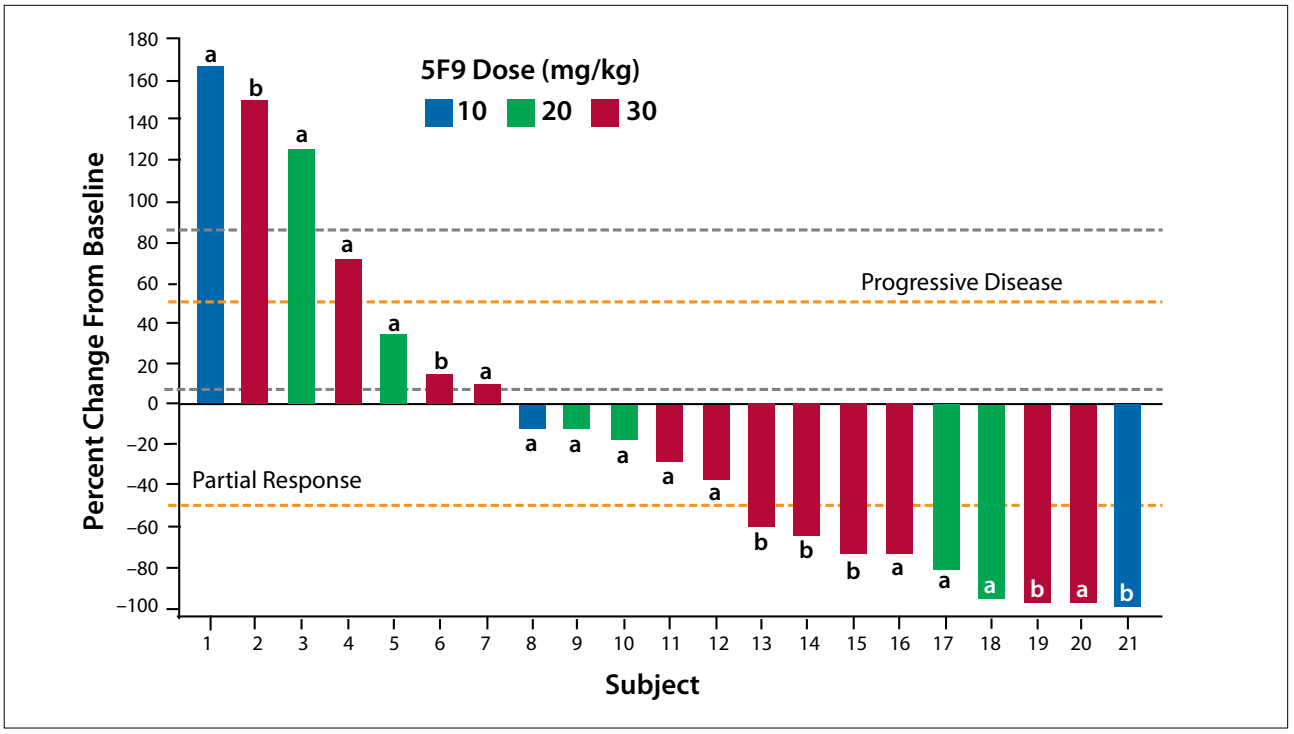

Figure 4. Antitumor activity in a trial of 5F9 plus rituximab. Partial response and progressive disease were defined according to the Lugano criteria. [a]DLBCL. [b]Follicular lymphoma. Adapted from Advani RH et al. ASCO abstract 7504. *J Clin Oncol*. 2018;36(15 suppl).[4]

375 mg/kg weekly for cycle 1, then monthly for cycles 2 to 6. The trial's primary endpoint was the safety, tolerability, and recommended phase 2 dose of the antibody combination.

The trial enrolled 22 patients with DLBCL and 7 with follicular lymphoma. Their median age was 59 years (range, 44-82 years), and 68% had stage III/IV disease. The median number of prior therapies was 4 (range, 2-10), and 95% of patients were refractory to their prior rituximab regimen. Thirteen patients were treated at the highest dose level of 5F9, and the maximum tolerated dose was not reached. Therefore, the recommended phase 2 dose in combination with rituximab was a priming dose of 1 mg/kg, followed by a maintenance dose of 30 mg/kg given weekly for cycle 1 and every 2 weeks for subsequent cycles.

The objective response rate (ORR) was 50% (according to Lugano criteria). The change in tumor burden is shown

ABSTRACT SUMMARY Two Years Rituximab Maintenance Vs Observation After First-Line Treatment With Bendamustine Plus Rituximab in Patients With Marginal Zone Lymphoma: Results of a Prospective, Randomized, Multicenter Phase 2 Study (the StiL NHL7-2008 MAINTAIN Trial)

Maintenance therapy with rituximab after treatment with bendamustine plus rituximab is the standard of care for first-line treatment of advanced indolent lymphomas, such as follicular lymphoma. However, rituximab maintenance is not commonly administered to patients with advanced marginal zone lymphoma. Two years of rituximab maintenance therapy was compared with observation after induction with bendamustine plus rituximab in patients with advanced marginal zone lymphoma (Abstract 7515). The patients' median age was 65 years (range, 25-80 years), and 78% had stage IV disease. After a median time of observation of 77.8 months, the 119 patients available for efficacy and safety analysis had an ORR of 91% after induction treatment, which included a CR rate of 19%. The study then randomly assigned 104 patients to rituximab maintenance or observation. The median PFS was not reached with rituximab maintenance vs 91.6 months with observation (HR, 0.33; 95% CI, 0.16-0.72; *P*=.005). The 6-year OS rate was similar for the 2 arms (92% with rituximab maintenance vs 86% with observation; HR, 0.54, 95% CI, 0.21-1.46; *P*=.231). Toxicities were consistent with prior observations, and no progressive multifocal encephalopathy was observed.

in Figure 4. Complete responses (CRs) were seen in 43% of patients with follicular lymphoma and 33% of those with DLBCL. Efficacy was observed among patients who were refractory to a prior rituximab-containing regimen. Most responses were observed within the first 2 months of treatment. After a median follow-up of 6 to 8 months, 11 patients had responded and 1 had developed progressive disease. In 2 DLBCL patients, response improved over time, from stable disease to a CR in one and from a partial response (PR) to a CR in the other. The median duration of response was not reached, and the longest observed duration of response exceeded 14 months.

Most AEs were grade 1 or 2. The most common AEs of any grade were, as anticipated, on-target anemia, infusion reactions, and related symptoms. Three patients developed dose-limiting toxicities. Two of these patients were successfully rechallenged and continued treatment, with resolution of the AE. One patient discontinued treatment owing to an AE. No autoimmune AEs were observed. There were no late safety signals, and treatment lasted for more than 18 months in some patients.

Depending on their age, red blood cells express proteins that may induce or inhibit phagocytosis and lead to on-target anemia. Older red blood cells lose expression of CD47 and gain expression of molecules that activate phagocytosis. Use of an initial priming dose of 5F9 results in a temporary, mild decline in hemoglobin caused by clearance of aged red blood cells and temporary compensatory reticulocytosis. In the current study, hemoglobin and reticulocyte levels returned to baseline with continued 5F9 treatment, after approximately 8 weeks. The recommended phase 2 dose is supported by data showing a CD47 receptor occupancy of nearly 100% on day 1 of cycle 2, combined with 5F9 tissue penetration observed via immunohistochemical staining. 5F9 recently received Fast Track designation by the FDA for both DLBCL and follicular lymphoma. Phase 2 studies of 5F9 plus rituximab are ongoing.[5]

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Brentuximab Vedotin With Chemotherapy for Stage III or IV Hodgkin Lymphoma: Impact of Cycle 2 PET Result on Modified Progression-Free Survival

The ECHELON-1 trial compared 6 cycles of brentuximab vedotin plus AVD vs ABVD in patients with treatment-naive, stage III/IV HL.[1] Interim PET imaging has been validated for response assessment in HL patients. A Deauville score of 3 or lower was considered PET-negative, and a score of 4 or 5 was PET-positive.[2-4] In a previous study of ABVD chemotherapy, PET2-positivity was prognostic for a reduced PFS.[5]

A post-hoc analysis of results from the ECHELON-1 trial evaluated clinical characteristics and modified PFS outcomes based on PET2 results as determined by an independent review facility.[6] Patients with a Deauville score of 5 at PET2 were allowed to switch to an alternative therapy at the physician's discretion. Rates of PET2 negativity were 89% (588/664) with brentuximab vedotin plus AVD and 86% (577/670) with ABVD. A positive PET2 result was seen in 7% of patients (47/644) treated with brentuximab vedotin plus AVD and in 9% (58/670) of those treated with ABVD. PET2 status was not available for 64 patients, and 5 patients had a Deauville score of 5 and switched to a different therapy. Patient characteristics were generally similar in both arms, regardless of PET2 status.

Among patients treated with brentuximab vedotin plus AVD, the estimated 2-year modified PFS was 85.2% for those who were PET2-negative vs 57.5% for those who were PET2-positive (HR, 3.382; 95% CI, 2.033-5.625; $P<.001$). In the ABVD arm, the estimated 2-year modified PFS was 80.9% for PET2-negative patients vs 42.0% for PET2-positive patients (HR, 4.793; 95% CI, 3.229-7.118; $P<.001$). The modified PFS was numerically superior with brentuximab vedotin plus AVD vs ABVD among PET2-negative patients (85.2% vs 80.9%; $P=.070$) and PET2-positive patients (57.5% vs 42.0%; $P=.089$;

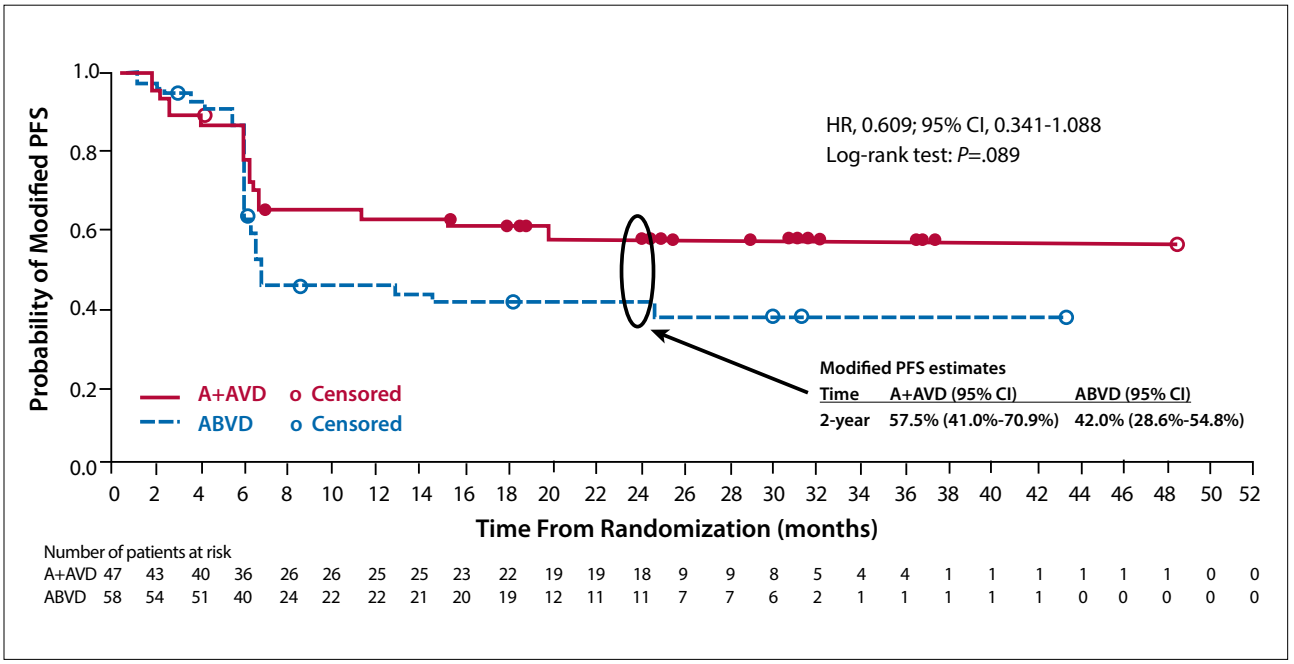

Figure 5. Modified PFS in a study of A+AVD vs ABVD per analysis from an independent review facility in PET2-positive patients. One patient in the A+AVD arm and 4 in the ABVD arm switched to alternative first-line therapy based on an unacceptable response. A+AVD, brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; HR, hazard ratio; PET2, positron emission tomography imaging performed after treatment cycle 2; PFS, progression-free survival. Adapted from Chen RW et al. ASCO abstract 7539. *J Clin Oncol.* 2018;36(15 suppl).[6]

Figure 5), but the comparisons did not reach statistical significance.

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ABSTRACT SUMMARY Acalabrutinib Alone or in Combination With Rituximab in Follicular Lymphoma

Acalabrutinib was evaluated with or without rituximab in a phase 1b/2 study of patients with follicular lymphoma (Abstract 7549). The study enrolled 13 patients with newly diagnosed follicular lymphoma and 27 with relapsed or refractory disease. All treatment-naive patients received the 2-drug combination. Previously treated patients were randomly assigned to acalabrutinib monotherapy or acalabrutinib plus rituximab. The median follow-up was 26.0 months (range, 3.7-27.2 months) for the treatment-naive cohort and 7.6 months (range, 0.7-26.7 months) for patients with relapsed or refractory disease. Among the 40 patients across all cohorts, the most common AEs of any grade were fatigue (48%), headache (43%), and diarrhea (40%). The most common grade 3 AEs were hypertension (8%), increased alanine transaminase (5%), increased aspartate transaminase (5%), and cellulitis (5%). One grade 4 AE of neutropenia was reported, and serious AEs occurred in 18% of patients. The ORR was 92% in treatment-naive patients. In patients with relapsed or refractory disease, the ORR was 33% with acalabrutinib (100 mg twice daily) vs 38% with acalabrutinib plus rituximab. The median duration of response was not reached for any of the 3 cohorts. Among patients with relapsed or refractory disease, the median PFS was 12.0 months with acalabrutinib monotherapy vs 8.3 months with the 2-drug combination. The median PFS was not reached for treatment-naive patients in either cohort.

Durability of Response in ZUMA-1, the Pivotal Phase 2 Study of Axicabtagene Ciloleucel in Patients With Refractory Large B-Cell Lymphoma

Axicabtagene ciloleucel is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy designed to increase the T-cell response against tumor cells.[1] The CAR construct consists of an anti-CD19 single-chain variable domain, a CD28 transmembrane domain, a CD28 costimulatory domain, and the CD3ζ T-cell receptor signaling domain. CD19 is a transmembrane glycoprotein that is expressed on the vast majority of normal and neoplastic B cells. The phase 1/2 ZUMA-1 trial (A Phase 1-2 Multi-Center Study Evaluating Axicabtagene Ciloleucel in Subjects With Refractory Aggressive Non-Hodgkin Lymphoma) evaluated CAR T-cell therapy in patients with refractory NHL, including DLBCL, transformed follicular lymphoma, and primary mediastinal B-cell lymphoma. The phase 1 portion of the study included 7 patients and yielded an ORR of 71% and a CR rate of 57%.[2]

The phase 2 portion of the trial enrolled 101 patients into 2 cohorts: those with refractory DLBCL (n=77) and those with refractory transformed follicular lymphoma or primary mediastinal B-cell lymphoma (n=24). Key eligibility criteria included aggressive B-cell lymphoma; no response to the most recent chemotherapy, or relapse within 12 months of an autologous stem cell transplant (SCT); and prior treatment with an anti-CD20 monoclonal antibody and an anthracycline. Patients received 3 days of a conditioning regimen consisting of cyclophosphamide (500 mg/m^2) plus fludarabine (30 mg/m^2). The axicabtagene ciloleucel dose was 2 × 10^6 CAR T cells/kg. CAR T cells were successfully manufactured for 99% of enrolled patients, and 91% of enrolled patients received treatment. Among the 108 patients in phase 1 or 2 of ZUMA-1 (at a data cutoff of August 17, 2017), the minimum follow-up was 12 months and the median follow-up was 15.4 months.[3] The long-term follow-up analysis showed an ORR of 82% and a CR rate of 58%, with ongoing responses in 42% of patients. The median OS was not reached. The median duration of response was 11.1 months (95% CI, 3.9 months to not reached). Grade 3 or higher AEs of interest included cytokine release syndrome (12%) and neurologic events (31%).

A retrospective analysis of the phase 2 ZUMA-1 data was conducted to evaluate whether the time to response and PR and CR at month 3 after treatment were prognostic factors for PFS.[4] The study was prompted by the fact that over half of the progression events in ZUMA-1 had occurred by month 3 after the CAR T-cell infusion. Among the 84 patients who had a PR or CR, the median time to response was 1 month (range, 0.8-14.8 months) overall, and 1 month (range, 0.8-12.3 months) for patients who achieved a CR (Figure 6). Among the 44 patients with a PR, 18 (42%) converted to a CR. Although many of the patients with a PR converted to a CR by month 3, conversions from a PR to a CR were observed up to 12 months after the CAR T-cell infusion.

Among the 101 patients in the phase 2 study, the median age was 58 years (range, 23-76 years), two-thirds were male, and 85% had stage III/IV disease. Most patients (69%) had received 3 or more prior therapies. Among the patients with a response at 3 months, 9 had a PR and 42 had a

ABSTRACT SUMMARY Immune Toxicity in Post Autologous Transplant Patients Treated With Brentuximab Vedotin in Combination With Immune Checkpoint Blockade

Data from the E4412 study (A Phase I Study With an Expansion Cohort of the Combinations of Ipilimumab, Nivolumab, and Brentuximab Vedotin in Patients With Relapsed/Refractory Hodgkin Lymphoma) were examined to assess the relationship between the use of checkpoint blockade after SCT and subsequent immunologic toxicity (Abstract 7538). Eighteen patients had undergone prior SCT (15 autologous and 3 allogeneic). Ten patients were treated with ipilimumab plus brentuximab vedotin (arms A-C), and 8 were treated with nivolumab plus brentuximab vedotin (arms D-F). The baseline demographic characteristics were similar for both patient cohorts. For patients in arms A to C, rates of grade 4 toxicity were 0% for those who had undergone SCT vs 4% for the overall cohort. Other toxicities that were higher in the overall cohort included grade 3 rash (39% vs 20%), allergic reaction (39% vs 20%), grade 1/2 diarrhea (69% vs 50%), and eye disorders (13% vs 10%). The rate of grade 2 rash was higher in the post-SCT patients (70% vs 39%). For patients in arms D, E, and F, rates of grade 4 or 5 toxicity were 16% for post-SCT patients vs 21% for the overall cohort of 19 patients. Rates of grade 4/5 pneumonitis were 16% for post-SCT patients vs 10% for the overall cohort, and grade 3 typhlitis was observed in 16% vs 5%, respectively.

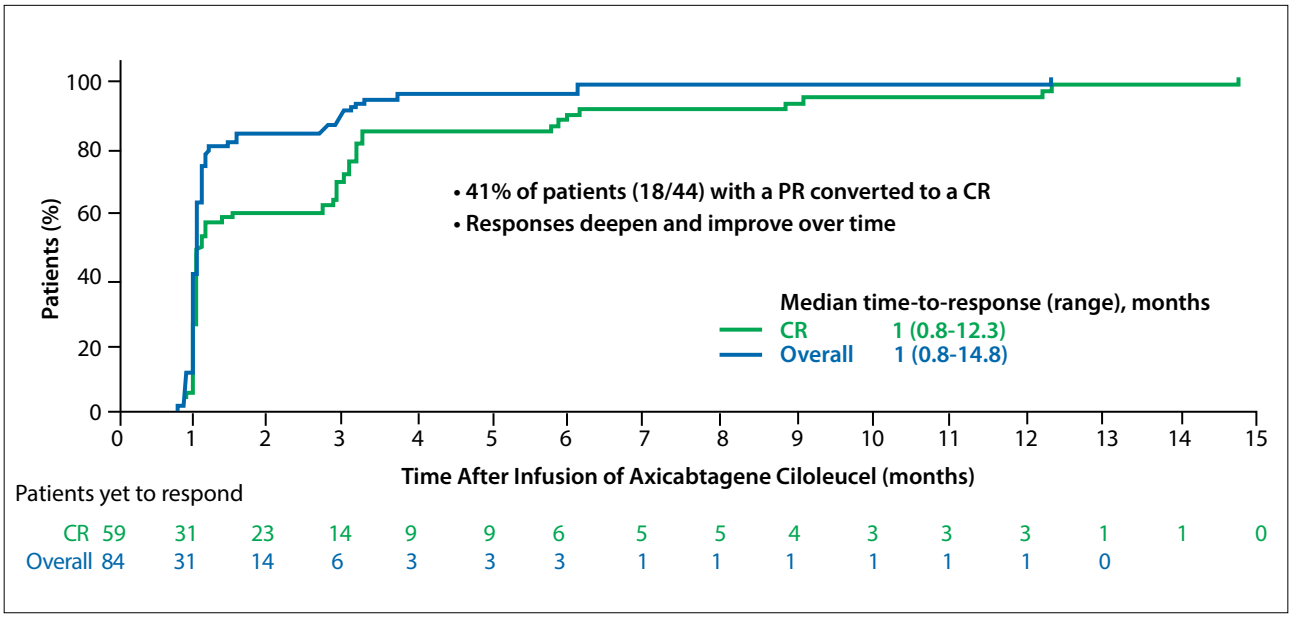

Figure 6. Time to objective response and complete response in a study of axicabtagene ciloleucel. CR, complete response; PR, partial response. Adapted from Locke FL et al. ASCO abstract 3003. *J Clin Oncol.* 2018;36(15 suppl).[4]

CR. Patients with a PR or CR shared similar characteristics, including the median number of prior therapies and the tumor burden. Kaplan-Meier analysis was conducted to determine the PFS rate for patients with a PR vs those with a CR at month 3 after treatment. The analysis yielded similar PFS rates for both groups. For patients with a CR at month 3, the median PFS was not reached (95% CI, not reached to not reached). For patients with a PR at month 3, the median PFS was also not reached (95% CI, 4.4 months to not reached). Among the patients with a PR or CR at month 3, the likelihood of maintaining that response at month 12 was 78% (95% CI, 36%-94%) and 79% (95% CI, 63%-88%), respectively.

Rates of grade 3 or higher AEs were 100% in patients who achieved a PR at month 3 after CAR T-cell infusion and 93% in those with a CR at this time. In comparison, the rate was 97% in the overall study population. Cytokine release syndrome of grade 3 or higher occurred in 0% of the PR group, 12% of the CR group, and 12% of the 101 patients included in the phase 2 portion of the trial. Neurologic events of grade 3 or higher were observed in 33% of patients with a PR at month 3, 36% of those with a CR at month 3, and 29% of the overall study population. The safety results led to the adoption of guidelines that recommend earlier intervention for cytokine release syndrome.[5]

ABSTRACT SUMMARY Dose-Adjusted EPOCH-R With High-Dose Methotrexate for Newly Diagnosed Stage II-IV CD5-Positive Diffuse Large B-Cell Lymphoma: Primary Analysis of the PEARL5 Study

Approximately 5% to 10% of DLBCL patients have CD5-positive disease, which is associated with aggressive clinical features and increased rates of central nervous system relapse. Standard immunochemotherapy yields reduced rates of survival in patients with CD5-positive DLBCL compared with CD5-negative DLBCL. The multicenter, phase 2 PEARL5 study (A Phase II Trial of DA-EPOCH and Rituximab With HD-MTX Therapy for Newly-Diagnosed DLBCL With CD5 Expression) evaluated dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R) with high-dose methotrexate in 47 patients with newly diagnosed, CD5-positive, stage II to IV DLBCL (Abstract 7561). Patients had a median age of 62 years (range, 37-74 years), and 53% had stage III/IV disease. After a median follow-up of 3.1 years (range, 2.0-4.9 years), the 2-year PFS rate was 79% (95% CI, 64%-88%). The result was superior to the historical control of 51% with rituximab plus chemotherapy. The 2-year OS rate was 79% (95% CI, 76%-95%). All 4 of the patients (9%) who experienced central nervous system relapse had activated B-cell type DLBCL. One of these patients had primary testicular DLBCL, and the other 3 experienced central nervous system relapse prior to administration of high-dose methotrexate. The time to central nervous system relapse ranged from 0.1 to 1.3 years, and survival ranged from 0.5 to 2.3 years.

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Long-Term Follow-Up of Brentuximab Vedotin ± Dacarbazine as First-Line Therapy in Elderly Patients With Hodgkin Lymphoma

Clinical trials of treatment-naive HL patients commonly exclude those who are ages 60 years or older. Compared with younger patients, elderly patients have an inferior prognosis, with a shorter survival and inferior outcome after first-line treatment. Dr Jonathan Friedberg presented 3-year follow-up results from a nonrandomized, open-label, phase 2 study that evaluated brentuximab vedotin (1.8 mg/kg, day 1) for up to 16 cycles with or without dacarbazine (375 mg/m^2, day 1) for up to 12 cycles.[1] The trial enrolled patients with classical HL, but excluded those with nodular lymphocyte-predominant HL. Patients were treatment-naive and ages 60 years or older. They had measurable disease and an Eastern Cooperative Oncology Group performance status of 0 to 3. Patients were ineligible for conventional first-line combination therapy or declined this treatment. The primary endpoint was the ORR.[2]

In this study, 49 patients received at least 1 dose of brentuximab vedotin, either as monotherapy (n=27) or with dacarbazine (n=22). In the monotherapy arm, 52% of patients were ineligible for conventional chemotherapy, 63% had stage III/IV disease, and 22% had extranodal involvement. Among patients in the combined treatment arm, 86% were ineligible for conventional chemotherapy, 73% had stage III/IV disease, and 41% had extranodal involvement. Comorbidities and functional status were generally similar in both arms.

The median observation time was 42.6 months (range, 4.6-56.3 months) for the monotherapy patients and 37.8 months (range, 14.8-44.8 months)

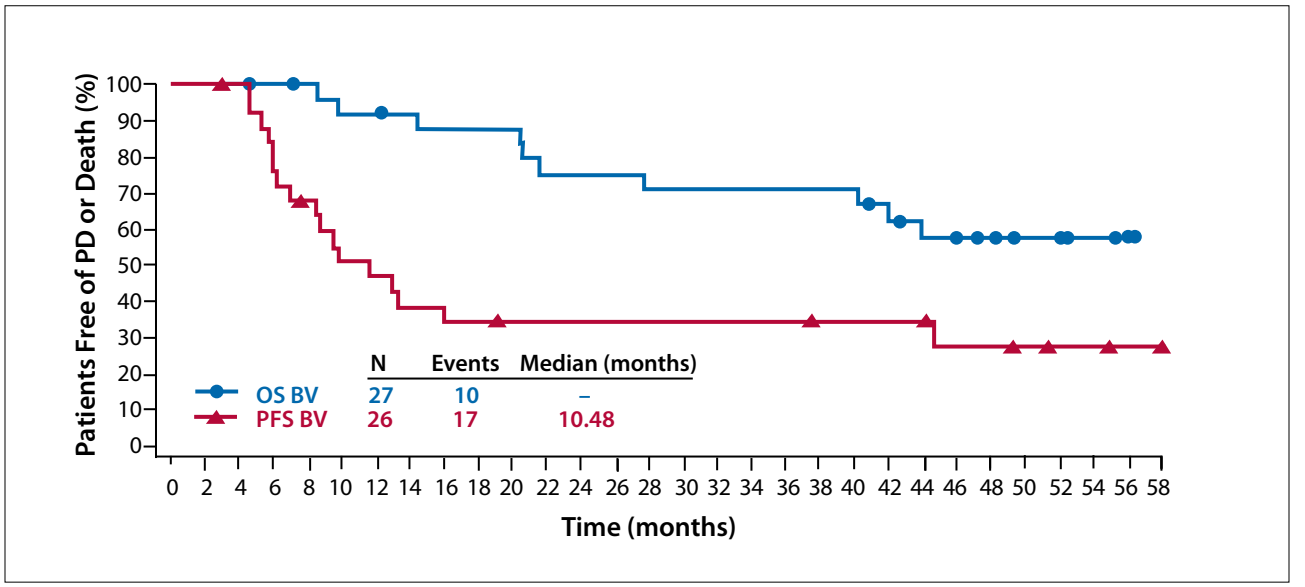

Figure 7. Overall survival and progression-free survival after treatment with brentuximab vedotin among elderly patients with Hodgkin lymphoma. BV, brentuximab vedotin; OS, overall survival; PD, progressive disease. Adapted from Friedberg JW et al. ASCO abstract 7542. *J Clin Oncol*. 2018;36(15 suppl).[1]

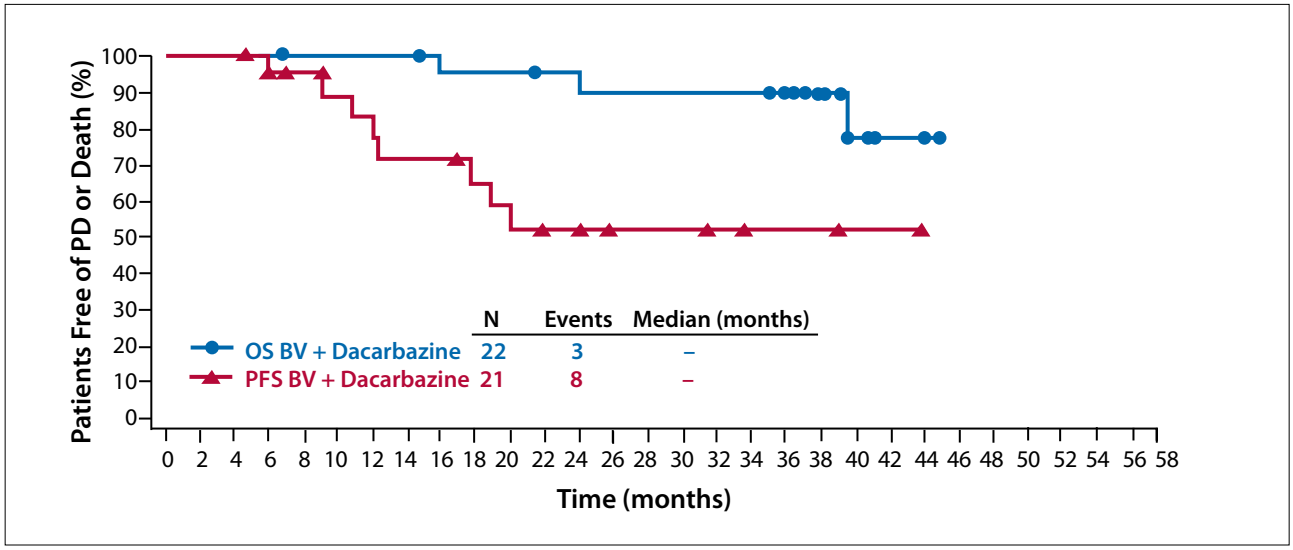

Figure 8. Overall survival and progression-free survival after treatment with brentuximab vedotin plus dacarbazine among elderly patients with Hodgkin lymphoma. BV, brentuximab vedotin; OS, overall survival; PD, progressive disease. Adapted from Friedberg JW et al. ASCO abstract 7542. *J Clin Oncol*. 2018;36(15 suppl).[1]

for the combination therapy patients. The estimated 3-year PFS was 34% (95% CI, 16%-53%) vs 52% (95% CI, 26%-73%), respectively (Figures 7 and 8). The estimated 3-year OS was 71% (95% CI, 49%-85%) with monotherapy vs 90% (95% CI, 65%-97%) with the combination.

The median time to resolution of associated symptoms was 15.0 weeks with monotherapy vs 3.6 weeks with the combination. However, peripheral neuropathy symptoms improved more quickly in the monotherapy arm (8.9 vs 14.0 weeks).

The median number of treatment cycles was 8 (range, 3-23) in the brentuximab vedotin monotherapy arm vs 12.5 (range, 2-27) in the combination arm. Treatment-emergent peripheral neuropathy events of any grade were observed in 89% vs 86%, respectively.[3,4] Grade 3 peripheral neuropathy events occurred in 27% to 30% of patients in the 2 arms, and no grade 4 events were reported.

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Cost-Effectiveness Analysis of Brentuximab Vedotin With Chemotherapy in Newly Diagnosed Stage III/IV Hodgkin Lymphoma

In the ECHELON-1 trial, AVD plus brentuximab vedotin improved survival and response outcomes vs standard ABVD, while also reducing rates of pulmonary toxicity.[1] A Markov decision-analytic model based on data from ECHELON-1 evaluated whether substitution of brentuximab vedotin for bleomycin in the ABVD regimen is cost-effective for patients with newly diagnosed stage III/IV HL.[2] Patients with previously untreated stage III/IV HL were included in a transition state model, which used 3-month length cycles, a lifetime horizon, and standard 3% future discounting. Transition probabilities and utilities were assessed using data from ECHELON-1 and previously published studies. The 2017 Medicare fee schedule and pertinent peer-reviewed medical literature were used to estimate baseline medical costs. Quality-adjusted life-years, incremental cost-effectiveness ratios, and lifetime direct health care costs were calculated for brentuximab vedotin plus AVD vs ABVD from a societal perspective within the United States. Drug calculations accounted for unused drug by rounding up to the next full single-use vial. The robustness of conclusions was tested using 1-way, probabilistic, and scenario analyses.

ABSTRACT SUMMARY Randomized Phase 2 Trial of Polatuzumab Vedotin With Bendamustine and Rituximab in Relapsed/Refractory FL and DLBCL

A randomized phase 2 trial investigated bendamustine and rituximab with or without polatuzumab vedotin in patients with relapsed or refractory DLBCL or grade 1, 2, or 3a follicular lymphoma (Abstract 7507). The study randomly assigned 80 patients with follicular lymphoma and 80 patients with DLBCL to the treatment arms. In follicular lymphoma patients, the ORR was 73% with bendamustine plus rituximab vs 77% with the polatuzumab vedotin combination. The median PFS was similar for both treatments (17.0-17.3 months; HR, 0.80). One-year PFS was 72% for bendamustine plus rituximab vs 84% for the polatuzumab vedotin combination. In patients with DLBCL, the ORR was 18% with bendamustine plus rituximab vs 45% when polatuzumab vedotin was added to treatment (*P*=.008), and the CR rate was 15% vs 40%, respectively (*P*=.012). Median PFS was significantly longer with the polatuzumab vedotin combination (6.7 vs 2.0 months; HR, 0.31; 95% CI, 0.18-0.55; *P*<.0001), as was median OS (11.8 vs 4.7 months; HR, 0.35; 95% CI, 0.19-0.67; *P*=.0008). In the overall study population, the most common AEs of grade 3 to 5 in the polatuzumab vedotin combination arm were cytopenias, febrile neutropenia, and infections. Serious AEs occurred more frequently in patients treated with the polatuzumab vedotin combination (55% vs 33%), and most commonly included infections (23% vs 18%) and febrile neutropenia (12% vs 3%). Rates of grade 5 AEs were similar (12% vs 11%).

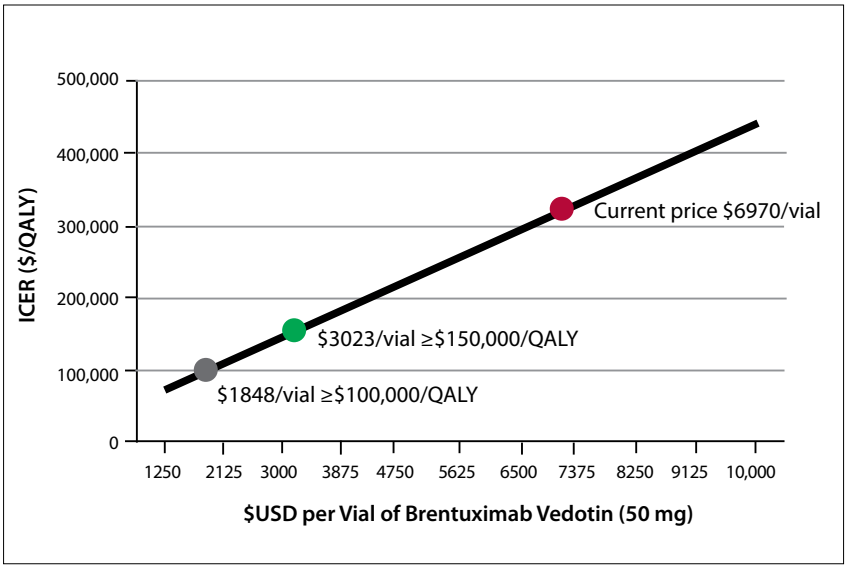

Figure 9. A model of indication-specific drug pricing showing the price reductions of brentuximab vedotin needed to reach an acceptable incremental cost-effectiveness ratio. Brentuximab vedotin was studied as a replacement for bleomycin in the ABVD regimen. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; $USD, US dollar. Adapted from Huntington SF et al. ASCO abstract 6609. *J Clin Oncol.* 2018;36(15 suppl).[2]

The model was used to estimate brentuximab vedotin price reductions that would lead to cost-effectiveness with indication-specific pricing.

The model showed improved long-term clinical outcomes with brentuximab vedotin plus AVD compared with ABVD, and an average gain of 1.34 life-years. Treatment with the brentuximab vedotin combination was associated with an incremental cost-effectiveness ratio of $317,254 per quality-adjusted life-year gained. Eliminating the need for growth factor support with brentuximab vedotin plus AVD yielded an incremental cost-effectiveness ratio of $249,640 per quality-adjusted life-year. Lifetime costs were estimated at $184,291 for ABVD and $361,137 for brentuximab vedotin plus AVD. The analysis assumed a current price of $6970 per 50 mg vial of brentuximab vedotin. With indication-specific pricing, the acquisition costs for brentuximab vedotin used for first-line treatment would have to be reduced by 56% (to $3023 per vial) to achieve a cost of $150,000 per quality-adjusted life-year and by 73% (to $1848 per vial) to reduce the cost to $100,000 per quality-adjusted life-year (Figure 9). Limitations to the study included the fact that, as in ECHELON-1, the model did not include alterations to first-line therapy based on interim PET results. In addition, the analysis evaluated only direct health care costs, without addressing the potential economic benefits that result from improved survival in a relatively young population.

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Highlights in Lymphoma From the 2018 American Society of Clinical Oncology Annual Meeting: Commentary

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The 2018 American Society of Clinical Oncology annual meeting featured several important abstracts on the management of lymphoma. Analyses of the ECHELON-1 trial (Phase 3 Frontline Therapy Trial in Patients With Advanced Classical Hodgkin Lymphoma) provided further insight into the use of brentuximab vedotin plus chemotherapy. Other studies evaluated the use of positron emission tomography (PET) to deescalate therapy after bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) and provided new data on chimeric antigen receptor (CAR) T-cell therapy and novel treatments.

Hodgkin Lymphoma

ECHELON-1

Dr Radhakrishnan Ramchandren presented an analysis of the North American population in the ECHELON-1 trial, which evaluated brentuximab vedotin plus chemotherapy in patients with newly diagnosed Hodgkin lymphoma.[1] Overall results from the trial, published in 2017, showed a modified progression-free survival (PFS) of 82.1% with brentuximab vedotin plus chemotherapy vs 77.2% with the control treatment of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), a difference of 4.9% (hazard ratio for an event of progression, death, or modified progression, 0.77; 95% CI, 0.60-0.98; *P*=.04).[2] ECHELON-1 enrolled approximately 1300 patients, of whom 500 lived in North America. Among these patients, half were treated with brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (AVD) and the other half received ABVD. The arms were well-balanced in terms of stage 3 or 4 disease, age, and International Prognostic Score. The analysis showed that the patients in North America did much better with brentuximab vedotin. The 2-year modified PFS, as assessed by an independent review facility, was 84.3% in patients receiving brentuximab vedotin plus AVD vs 73.7% in those receiving ABVD. This difference of 11.6% was statistically significant and dramatically different from that seen in the overall study population. Another important finding was the rate of 2-year PFS as assessed by the investigators, which was 88.1% with brentuximab vedotin plus AVD vs 76.4% with ABVD, a statistically significant difference of 11.7%. The presentation did not offer speculation as to why patients in North America did much better with brentuximab vedotin plus AVD vs ABVD.

I presented another subanalysis of the ECHELON-1 study. These data focused on the impact of cycle 2 PET (PET2) results on modified PFS in patients with stage 3 or 4 Hodgkin lymphoma treated with brentuximab vedotin plus chemotherapy.[3] It is known that patients treated with ABVD who are PET-positive after 2 cycles of therapy will not do well.[4] In ECHELON-1, outcomes to 6 cycles of ABVD according to PET2 results were similar to historical rates. The modified 2-year PFS was 42.0% among PET-positive patients vs 80.9% for PET-negative patients. After 2 cycles of brentuximab vedotin plus AVD, the modified 2-year PFS was 57.5% in the PET-positive group vs 85.2% in the PET-negative patients. Although this difference was not statistically significant, there appears to be an advantage to brentuximab vedotin plus AVD in PET2-positive patients.

Previously, one way to improve outcome in PET2-positive patients was to escalate therapy from ABVD to escalated BEACOPP after PET2. However, BEACOPP is associated with significant hematologic and infectious toxicities.[5] In a trial from the Southwest Oncology Group (SWOG), escalation of therapy resulted in a 2-year PFS of approximately 60%.[6] Based on this analysis of the ECHELON-1 trial, it may be possible to avoid escalated BEACOPP after PET2 by starting therapy with brentuximab vedotin plus AVD.

Another analysis of the ECHELON-1 trial, presented by Dr David Straus, evaluated the use of granulocyte-colony stimulating factor (G-CSF) prophylaxis among patients treated with brentuximab vedotin.[7] The design of ECHELON-1 did not mandate prophylactic G-CSF at initiation. Treatment with traditional ABVD also does not require primary G-CSF prophylaxis. During the trial, however, increased rates of febrile neutropenia in the experimental arm led to the recommendation of primary G-CSF prophylaxis. Eighty-three patients received primary G-CSF prophylaxis, and 453 did not. Most patients received the short-acting, nontabulated formulation. After institution of primary G-CSF prophylaxis, the rate of neutropenia decreased from 73% to 35%, and the rate of grade 3 or higher neutropenia dropped from 70% to 29%. Grade 4 neutropenia decreased from 51% to 22%. Most importantly, febrile neutropenia decreased from 21% to 11%. During cycle 1, febrile neutropenia decreased from 11% to 1%.

An interesting observation was

that patients who received primary G-CSF prophylaxis had far fewer dose delays of brentuximab vedotin plus AVD compared with patients without prophylaxis, at 35% vs 49%. This difference could explain the improvement in PFS seen with primary G-CSF prophylaxis. The 2-year modified PFS was 84.6% with primary G-CSF prophylaxis vs 81.7% without. (In comparison, the 2-year modified PFS was 77.2% in the ABVD arm.) Patients who received primary G-CSF prophylaxis had fewer dose delays and experienced less toxicity, and therefore they could tolerate more treatment administered on time, possibly leading to better outcomes.

Use of PET Scans to Deescalate BEACOPP

Dr Olivier Casasnovas presented the final analysis of the AHL2011 LYSA trial (Advanced Hodgkin Lymphoma 2011 Lymphoma Study Association), which evaluated whether results from PET scans can be used to deescalate therapy after escalated BEACOPP.[8] Outside the United States, one standard treatment for patients with advanced-stage Hodgkin lymphoma is escalated BEACOPP.[9] The associated toxicity,[5] however, has prompted evaluation of other strategies. In the AHL2011 LYSA trial, patients who were PET-negative after 2 cycles of escalated BEACOPP could downgrade to ABVD. In the standard arm, the interim PET result did not impact treatment; patients received 6 cycles of escalated BEACOPP. The Deauville score was used to categorize the scans, with scores of 1, 2, or 3 as negative and scores of 4 or 5 as positive. Overall, the PET2-negative rate was 87%. The 4-year PFS was 87.1% among patients in the experimental arm, in which the PET result was used to deescalate therapy, vs 87.4% in the standard arm, in which patients received 6 cycles of escalated BEACOPP. There was also no significant difference between the rates of 4-year overall survival, which were 97.1% vs 96.9%, respectively. The study therefore showed that deescalation of therapy based on a PET scan did not reduce PFS or overall survival. As expected, safety improved in the PET-driven arm, with decreased rates of anemia, febrile neutropenia, thrombocytopenia, infection, and sepsis. These patients also showed improvement in the rates of serious adverse events and secondary primary malignancies.

Non-Hodgkin Lymphoma

Polatuzumab Vedotin

Polatuzumab vedotin is an antibody drug conjugate targeting lymphomas that express CD79b, such as follicular lymphoma and DLBCL. A phase 1 trial showed high response rates with this drug as a single agent in patients with relapsed or refractory non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia.[10] Dr Laurie Sehn reported the results of a randomized phase 2 trial evaluating the addition of polatuzumab vedotin to bendamustine and rituximab in patients with refractory follicular lymphoma or diffuse large B-cell lymphoma (DLBCL).[11] The primary endpoint was the rate of complete response as assessed by an independent review facility. The addition of polatuzumab vedotin did not improve outcome among patients with follicular lymphoma. Improvement was seen, however, in the DLBCL cohort. The overall response rate was 45% with the addition of polatuzumab vedotin vs 18% with bendamustine and rituximab alone. The complete response rate was also higher with polatuzumab vedotin, at 40%, vs 15% with bendamustine and rituximab alone. The median PFS was 6.7 months vs 2.0 months, respectively, and the overall survival was 11.8 months vs 4.7 months. Based on these data, polatuzumab vedotin received breakthrough therapy designation and priority medicine designation by the US Food and Drug Administration (FDA) and European Medicines Agency for relapsed/refractory DLBCL. This agent could soon become an option for these patients.

A phase 1b study presented by Dr Ranjana Advani evaluated the first-in-class, anti-CD47 antibody known as 5F9 in combination with rituximab in patients with relapsed/refractory NHL.[12] CD47 is a "do not eat me" signal on cancer cells that prevents macrophages, a component of the innate immune system, from destroying the cells. When macrophages encounter CD47, they leave the cell intact. Among patients with DLBCL, those with low CD47 expression have better outcomes than those with high expression.[13]

Preclinical studies of NHL xenograft models found synergy between 5F9 and rituximab in inducing remissions.[13,14] This phase 1 trial evaluated 3 different doses of 5F9 in combination with rituximab. Patients had relapsed/refractory DLBCL or follicular lymphoma. The study found that 5F9 was safe through cohort 3, which evaluated a priming dose of 1 mg/kg, followed by a 30 mg/kg maintenance dose weekly for cycle 1, and then every 2 weeks for cycle 2 and subsequent treatment. This regimen became the recommended phase 2 dose.

The treatment was well-tolerated. Most adverse events were grade 1 or 2. The most common adverse events were, as expected, on-target anemia and infusion reaction. For all patients, the overall response rate was 50%, with a complete response rate of 36%. These rates were 40% and 33%, respectively, in the DLBCL cohort, and 71% and 43% in those with follicular lymphoma. Some durable responses were seen. 5F9 has received fast-track designation by the FDA for both DLBCL and follicular lymphoma.

Acalabrutinib

Dr Roger Owen presented results from a phase 2 trial of acalabrutinib in patients with relapsed/refractory or treatment-naive Waldenström macroglobulinemia.[15] Acalabrutinib is a newer-generation Bruton tyrosine kinase (BTK) inhibitor with highly selective, potent activity. It is more

selective for BTK than ibrutinib, an approved BTK inhibitor with demonstrated activity in Waldenström macroglobulinemia. In the study by Dr Owen, the overall response rate was 93%, and 80% of patients had a major response (defined as a partial response or better). In the treatment-naive population, the overall response rate was 93%, with a major response rate of 79%. The median duration of response was not reached. At 24 months, responses were maintained in 82% of the relapsed/refractory patients and 90% of the treatment-naive population. The 24-month PFS was 82% vs 90%, respectively.

Acalabrutinib was well-tolerated, with no unexpected toxicities. Most adverse events were grade 1 or 2, and the most common included headaches, diarrhea, contusions, dizziness, and fatigue. A key event of clinical interest was atrial fibrillation, which occurred in 4 patients with relapsed/refractory disease and 1 patient with treatment-naive disease. During treatment, patients' hemoglobin improved and immunoglobulin M decreased, which would be expected. In conclusion, acalabrutinib monotherapy was highly effective in patients with relapsed/refractory or treatment-naive Waldenström macroglobulinemia. The responses appeared to be durable.

Rituximab Maintenance

Dr Mathias Rummel presented data from a study of patients with marginal zone lymphoma who were treated with rituximab and bendamustine, and then randomly assigned to placebo or rituximab maintenance.[16] Maintenance rituximab improved PFS compared with placebo, with a hazard ratio of 0.33 and a *P* value of .00005. Previous studies showed that rituximab maintenance improved PFS in patients with follicular lymphoma,[17] and this new trial now provides data for marginal zone lymphoma.

Axicabtagene Ciloleucel

The ZUMA-1 trial (A Phase 1-2 Multi-Center Study Evaluating Axicabtagene Ciloleucel in Subjects With Refractory Aggressive Non-Hodgkin Lymphoma) evaluated the CAR T-cell therapy axicabtagene ciloleucel in patients with relapsed/refractory DLBCL. The trial met its primary endpoint, with an objective response rate of 82%.[18] The complete response rate was 54%. Based on these results, axicabtagene ciloleucel was approved by the FDA in this setting. Dr Frederick Locke presented a long-term analysis of ZUMA-1.[19] It was known that patients with a complete response did well. In contrast, among patients with a partial response, the response was not durable. In some cases, a partial response converted to a complete response. The long-term analysis found that 42% of patients had ongoing responses. The study also found that the PFS at 3 months is a predictor of long-term outcome; the response can be durable in patients who maintain a response at 3 months. Patients who do not have a response at 3 months are unlikely to stay in remission. This analysis therefore introduces 3-month PFS as an important clinical marker for these patients.

Disclosure

Dr Chen is a member of the speakers bureau of Seattle Genetics and a consultant for Seattle Genetics and Acerta.

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