

A SPECIAL MEETING REVIEW EDITION

Highlights in Hodgkin Lymphoma From the 62nd American Society of Hematology Annual Meeting and Exposition

A Review of Selected Presentations From the All-Virtual 62nd ASH Meeting and Exposition • December 5-8, 2020

Special Reporting on:

- Frontline Brentuximab Vedotin as Monotherapy or in Combination for Older Hodgkin Lymphoma Patients
- Phase II Study of Pembrolizumab Plus Gemcitabine, Vinorelbine, and Liposomal Doxorubicin as Second-Line Therapy for Relapsed or Refractory Classical Hodgkin Lymphoma
- Consolidation With Nivolumab and Brentuximab Vedotin After Autologous Hematopoietic Cell Transplantation in Patients With High-Risk Hodgkin Lymphoma
- Preliminary Results of a Phase 2 Study of Camidanlumab Tesirine (Cami), a Novel Pyrrolobenzodiazepine-Based Antibody-Drug Conjugate, in Patients With Relapsed or Refractory Hodgkin Lymphoma
- Brentuximab Vedotin With Chemotherapy for Patients With Previously Untreated, Stage III/IV Classical Hodgkin Lymphoma: 5-Year Update of the ECHELON-1 Study
- Everolimus Plus Itacitinib in Relapsed/Refractory Classical Hodgkin Lymphoma: Results of a Phase I/II Investigator Initiated Trial (EVITA Study)
- PET-Guided Strategy Improves the Safety of BEACOPP-Based Treatment in Advanced Hodgkin Lymphoma: Prolonged Follow-up of the Lysa AHL 2011 Phase 3 Study
- Survival Outcomes for US and Canadian Patients Diagnosed With Hodgkin Lymphoma Before and After Brentuximab Vedotin Approval for Relapsed/Refractory Disease: A Retrospective Cohort Study

PLUS Meeting Abstract Summaries

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ECHELON-1 TRIAL
5-YEAR DATA UPDATE
STAGE III/IV cHL

LASTING REMISSION THE FIRST TIME AROUND

Consistent benefit at 5 years vs ABVD

Get a snapshot of the 5-year
data on the following pages

- Primary endpoint: modified PFS per IRF—HR: 0.77 (95% CI: 0.60, 0.98); $P = 0.035$; median follow-up: 24.6 months¹
- Prespecified exploratory endpoint: PFS per INV at 5 years—HR: 0.68 (95% CI: 0.53, 0.87); not in approved labeling; supportive clinical information only²

ECHELON-1 trial design: A randomized, open-label trial of ADCETRIS+AVD vs ABVD in 1334 adult patients with newly diagnosed Stage III/IV cHL. Primary endpoint was modified PFS per IRF, defined as progression, death due to any cause, or receipt of additional anticancer therapy for patients not in complete remission after first-line therapy. Key secondary endpoint was OS. Prespecified exploratory endpoint was 5-year PFS per INV, defined as progression or death due to any cause.^{2,3}

Indication

ADCETRIS is indicated for the treatment of adult patients with previously untreated Stage III/IV classical Hodgkin lymphoma (cHL) in combination with doxorubicin, vinblastine, and dacarbazine.

Select 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).

ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; AVD = doxorubicin, vinblastine, dacarbazine; CI = confidence interval; HR = hazard ratio; INV = investigator; IRF = independent review facility; OS = overall survival; PFS = progression-free survival.

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.
- **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.

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

 CD30-DIRECTED
ADCETRIS[®]
brentuximab vedotin | for injection

ECHELON-1 PRIMARY ENDPOINT

A+AVD showed superior efficacy over ABVD at 2 years¹



23%

REDUCTION IN EVENT RISK¹

- Modified PFS per IRF (intent-to-treat population)*
- HR (95% CI): 0.77 (0.60, 0.98); $P = 0.035$; median follow-up: 24.6 months

MOST COMMON AND SERIOUS adverse reactions with A+AVD in ECHELON-1¹

- Most common serious adverse reactions: febrile neutropenia (17%), pyrexia (7%), neutropenia (3%), and pneumonia (3%)
- Most common adverse reactions ($\geq 20\%$): peripheral neuropathy, neutropenia, nausea, constipation, vomiting, fatigue, diarrhea, pyrexia, alopecia, decreased weight, abdominal pain, anemia, and stomatitis

33% REDUCTION

in the need for salvage chemotherapy and transplant³

In ECHELON-1, some patients required subsequent therapy:

- Patients requiring salvage chemotherapy:

66 for A+AVD, 99 for ABVD

- Patients receiving high-dose chemotherapy + HSCT:

36 for A+AVD, 54 for ABVD

This analysis was evaluated in ECHELON-1 but is not included in the approved product labeling. This analysis was not prespecified. Data are provided as supportive clinical information.

Select Important Safety Information (cont'd)

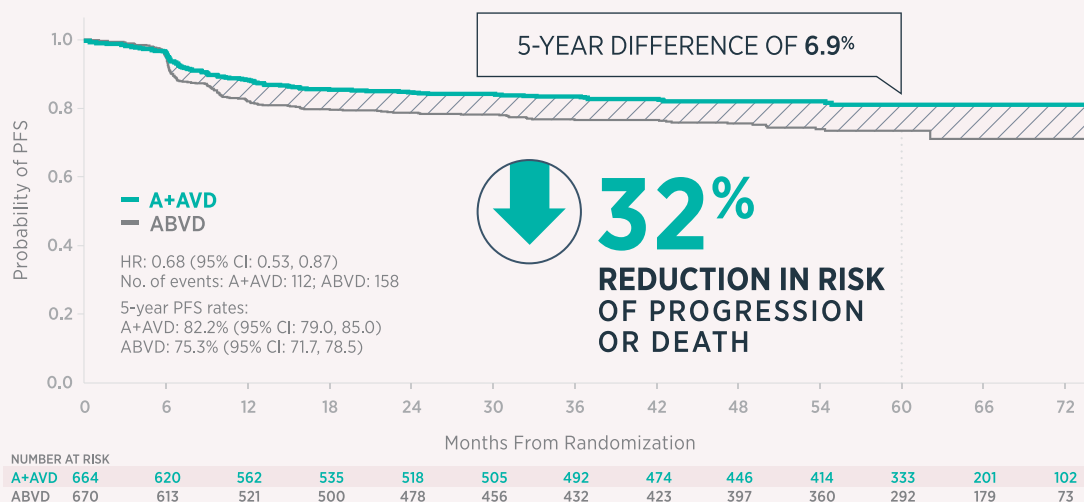
Warnings and Precautions

- **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 beginning with Cycle 1 for patients who receive ADCETRIS in combination with chemotherapy for previously untreated Stage III/IV cHL or previously untreated PTCL. 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 \geq 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 \geq Grade 3 adverse reactions and deaths was greater in patients with moderate or severe hepatic impairment compared to patients with normal hepatic function. Avoid 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

A+AVD offers the best chance at living relapse-free at 5 years vs ABVD

The 5-year data provided are not contained in the approved product labeling. 5-year PFS per INV was a prespecified exploratory analysis. Data are provided as supportive clinical information.

A+AVD showed an ~7% PFS per INV benefit over ABVD at 5 years²



- OS, a key secondary endpoint, not reached at 5 years²

Discover more data at adcetrispro.com

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.

- **Hyperglycemia:** Serious cases, such as new-onset hyperglycemia, exacerbation of preexisting diabetes mellitus, and ketoacidosis (including fatal outcomes) have been reported with ADCETRIS. Hyperglycemia occurred more frequently in patients with high body mass index or diabetes. Monitor serum glucose and if hyperglycemia develops, administer anti-hyperglycemic medications as clinically indicated.
- **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% in any study) Adverse Reactions

Peripheral neuropathy, fatigue, nausea, diarrhea, neutropenia, upper respiratory tract infection, pyrexia, constipation, vomiting, alopecia, decreased weight, abdominal pain, anemia, stomatitis, lymphopenia, and mucositis.

Drug Interactions

Concomitant use of strong CYP3A4 inhibitors or inducers 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 the following pages. Full Prescribing Information is available at adcetrispro.com


*Patients were randomized 1:1 to A+AVD (n = 664) or ABVD (n = 670) then received treatment on Days 1 and 15 of each 28-day cycle for up to 6 cycles.¹

[†]At the time of the modified PFS analysis, an interim OS analysis did not demonstrate a significant difference.^{1,3}

A+AVD = ADCETRIS + doxorubicin, vinblastine, dacarbazine; HSCT = hematopoietic stem cell transplantation.

References: 1. ADCETRIS [Prescribing Information]. Bothell, WA: Seattle Genetics, Inc. October 2019. 2. Straus DJ, Dlugosz-Danecka M, Connors JM, et al. Brentuximab vedotin with chemotherapy for patients with previously untreated, stage III/IV classical Hodgkin lymphoma: 5-year update of the ECHELON-1 study. Poster presented at: 62nd Annual Meeting of the American Society of Hematology; December 5-8, 2020. 3. 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.



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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 doxorubicin, vinblastine, and dacarbazine.

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 a 30-minute intravenous infusion.

The recommended dose is 1.2 mg/kg up to a maximum of 120 mg in combination with doxorubicin, vinblastine, and dacarbazine (AVD), administered every 2 weeks until a maximum of 12 doses, disease progression, or unacceptable toxicity. Reduce the dose in patients with mild hepatic impairment (Child-Pugh A) to 0.9 mg/kg up to a maximum of 90 mg every 2 weeks. 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 ECHELON-1 (Study 5), 67% of patients treated with ADCETRIS+AVD experienced any grade of neuropathy. The median time to onset of any grade was 2 months (range, 0-7), of Grade 2 was 3 months (range, 0-6), and of Grade 3 was 4 months (range, <1-7). The median time from onset to resolution or improvement of any grade was 2 months (range, 0-32), of Grade 2 was 3 months (range, 0-28), and of Grade 3 was 4 months (range, 0-32). Of these patients, 43% had complete resolution, 24% had partial improvement (a decrease in severity by one or more grades 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 had Grade 1 (36%), Grade 2 (16%), Grade 3 (4%), or Grade 4 (<1%) neuropathy.

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

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

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

5.8 Hepatotoxicity

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 Hyperglycemia

Serious events of hyperglycemia, such as new-onset hyperglycemia, exacerbation of preexisting diabetes mellitus, and ketoacidosis (including fatal outcomes) have been reported in ADCETRIS-treated patients. In studies of ADCETRIS monotherapy, 8% of patients experienced any grade hyperglycemia, with 6% experiencing Grade 3 or 4 hyperglycemia. The median time to onset for any grade or Grade 3 or 4 was 1 month (range 0-10). Hyperglycemia occurred more frequently in patients with high body mass index or diabetes. Monitor serum glucose and if hyperglycemia develops, administer anti-hyperglycemic medications as clinically indicated.

5.14 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. In animal reproduction studies, brentuximab vedotin caused embryo-fetal toxicities, including significantly decreased embryo viability, and fetal malformations 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 most common adverse reactions (≥20%) in combination with AVD were peripheral neuropathy, neutropenia, nausea, constipation, vomiting, fatigue, diarrhea, pyrexia, alopecia, decreased weight, abdominal pain, anemia, and stomatitis.

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

ADCETRIS in combination with AVD 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)

Adverse Reaction	ADCETRIS+AVD Total N = 662 % of patients			ABVD Total N = 659 % of patients		
	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	-

Adverse Reaction	ADCETRIS+AVD Total N = 662 % of patients			ABVD Total N = 659 % of patients		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
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 in combination with AVD (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 in combination with AVD (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 monotherapy. 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: non-infectious 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 systemic anaplastic large cell lymphoma (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.

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 ($\geq 99\%$), post-implantation loss ($\geq 99\%$), decreased numbers of live fetuses, and external malformations (i.e., umbilical hernias and malrotated hindlimbs). Systemic exposure in animals at the brentuximab vedotin dose of 3 mg/kg is approximately the same exposure in patients with 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 AVD 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.

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.

Hyperglycemia: Educate patients about the risk of hyperglycemia and how to recognize associated symptoms.

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



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Frontline Brentuximab Vedotin as Monotherapy or in Combination for Older Hodgkin Lymphoma Patients

Older patients with relapsed/refractory classical Hodgkin lymphoma have high rates of response and encouraging progression-free survival (PFS) when treated with brentuximab vedotin as monotherapy or in combination with other single agents, according to the results of a phase 2 study presented by Dr Christopher A. Yasenchak.¹ Outcomes with standard chemotherapy in patients ages 60 years and older are markedly inferior to those in younger patients because of intrinsic differences in disease biology, as well as increased rates of baseline comorbidities, advanced disease, and treatment-related morbidity and mortality.²⁻⁴ In previous studies of patients ages 60 years and older with relapsed/refractory classical Hodgkin lymphoma, single-agent brentuximab vedotin achieved high response rates,⁵ and in combination with nivolumab, it produced objective response rates (ORRs) reaching 95%.^{6,7}

The current study evaluated brentuximab vedotin at 1.8 mg/kg admin-

istered every 3 weeks for up to 16 cycles, either as a single agent (n=26) or in combination with dacarbazine at 375 mg/m² (n=20), bendamustine at 70 mg/m² (n=20), or nivolumab at 3 mg/kg (n=21). The patients' median age was 74 years (range, 60-92).

The ORR was 92% (complete response [CR] rate, 72%) with brentuximab vedotin as a single agent. For the combination regimens, the ORR was 100% (CR rate, 68%) with dacarbazine, 100% (CR rate, 88%) with bendamustine, and 95% (CR rate, 79%) with nivolumab. The median PFS was 10.4 months, 47 months, 40 months, and not reached, respectively (Figure 1). The median overall survival was 8.2 months with single-agent brentuximab vedotin, 46.9 months with the bendamustine combination, and not reached with the dacarbazine and nivolumab combinations (Figure 2).

Enrollment in the bendamustine arm closed early owing to multiple acute toxicities. Grade 3 or higher treatment-related adverse events (AEs)

occurred in 50% of the group treated with brentuximab vedotin as a single agent and in 40% of the dacarbazine group, 80% of the bendamustine group, and 62% of the nivolumab group. Peripheral neuropathy was the most common AE (27%, 25%, 15%, 19%). Serious treatment-related AEs occurred in 12%, 15%, 45%, and 5% of the patients, respectively. No treatment-related deaths occurred. Treatment discontinuation due to related AEs occurred in 42%, 40%, 60%, and 38% of patients, respectively.

The study investigators concluded that brentuximab vedotin monotherapy and combination therapy can be considered for older patients with relapsed/refractory classical Hodgkin lymphoma for whom conventional chemotherapy is unsuitable. Additional long-term follow-up is ongoing.

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Figure 1. Progression-free survival in a phase 2 study of frontline brentuximab vedotin as monotherapy or in combination with other agents for older patients with Hodgkin lymphoma. NR, not reached. Adapted from Yasenchak C et al. ASH abstract 471. *Blood*. 2020;136(suppl 1).¹

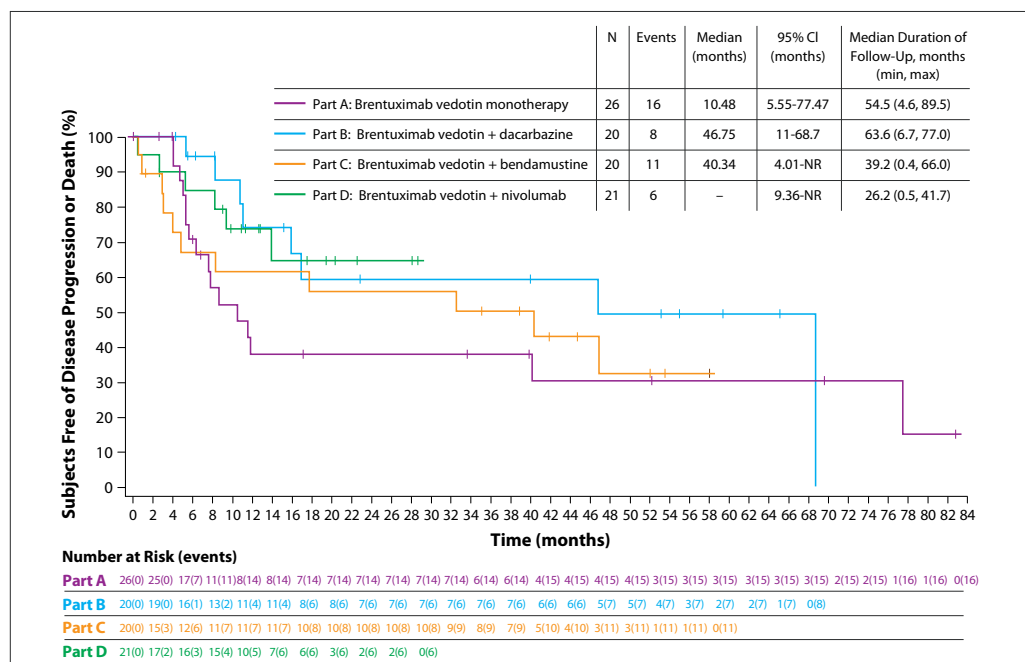
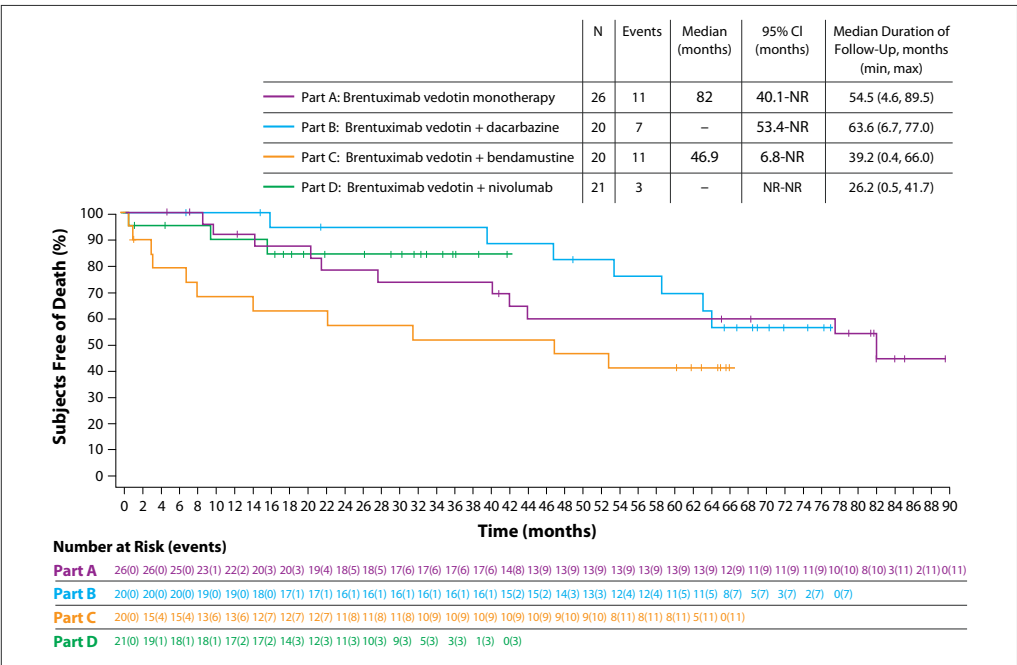


Figure 2. Overall survival in a phase 2 study of frontline brentuximab vedotin as monotherapy or in combination with other agents for older patients with Hodgkin lymphoma. NR, not reached. Adapted from Yasenchak C et al. ASH abstract 471. *Blood*. 2020;136(suppl 1).¹



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Phase II Study of Pembrolizumab Plus Gemcitabine, Vinorelbine, and Liposomal Doxorubicin as Second-Line Therapy for Relapsed or Refractory Classical Hodgkin Lymphoma

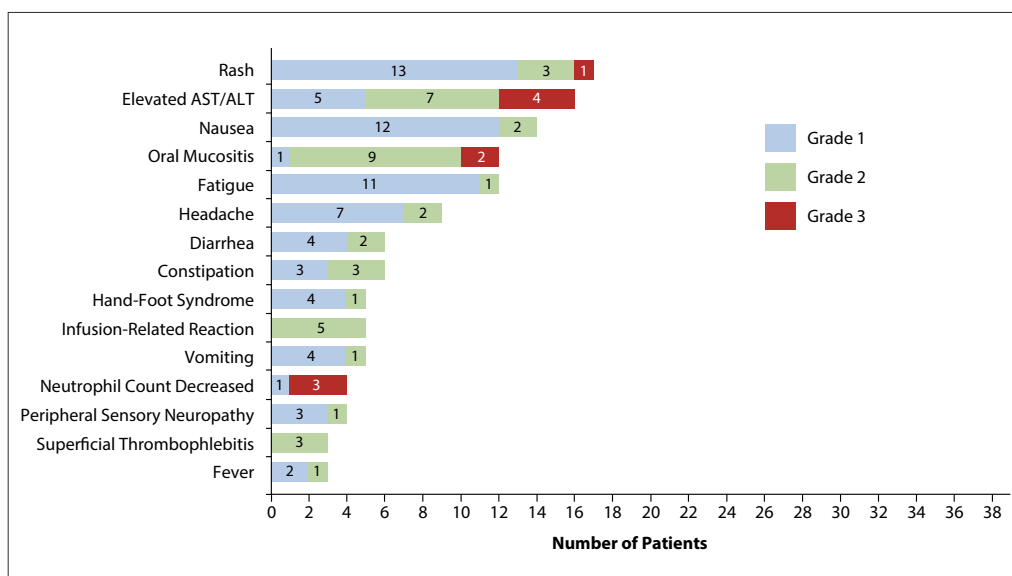
Second-line therapy with pembrolizumab plus gemcitabine, vinorelbine, and liposomal doxorubicin (pembrolizumab-GVD) is a highly effective and well-tolerated regimen that can be used efficiently to bridge patients with relapsed/refractory classical Hodgkin lymphoma to high-dose consolidation and autologous stem cell transplant (ASCT), according to data from a phase 2 study presented by Dr Alison J. Moskowitz.¹ No standard regimen exists for second-line therapy in classical Hodgkin

lymphoma. Options include regimens containing platinum, gemcitabine, and brentuximab vedotin. CR rates achieved with these regimens range from 50% to 70%.²⁻¹⁰ Brentuximab vedotin is being used increasingly in the frontline setting; therefore, effective second-line regimens that do not include this agent are needed. Pembrolizumab is an inhibitor of programmed death 1 (PD-1) that appears to be highly active in the setting of relapsed/refractory disease.^{10,11}

The study enrolled transplant-

eligible patients with relapsed/refractory classical Hodgkin lymphoma after induction therapy. The regimen consisted of a 21-day cycle in which the following agents were administered intravenously (IV): pembrolizumab at 200 mg on day 1, gemcitabine at 1000 mg/m² on days 1 and 8, vinorelbine at 20 mg/m² on days 1 and 8, and liposomal doxorubicin at 15 mg/m² on days 1 and 8. Patients with a CR (Deauville score ≤3) according to positron emission tomography (PET) after 2 or 4 cycles proceeded to consolidation with

Figure 3. Adverse events in a phase 2 study of pembrolizumab plus gemcitabine, vinorelbine, and liposomal doxorubicin as second-line therapy for relapsed or refractory classical Hodgkin lymphoma. ALT, alanine aminotransferase; AST, aspartate aminotransferase. Adapted from Moskowitz A et al. ASH abstract 470. *Blood*. 2020;136(suppl 1).¹



high-dose therapy and ASCT. The primary endpoint was the CR rate after 2 or 4 cycles of pembrolizumab-GVD.

Among 39 enrolled patients, 59% had stage III/IV disease, 31% had extranodal disease, 41% had prior refractory disease, and 38% had recurrent disease within 12 months after induction treatment. The median age was 31 years (range, 21-71), and 54% were female. Of the 2 patients not included in the analysis, one was still receiving the first 2 cycles of treatment and the other was found to have composite lymphoma.

Thirty-seven patients were evaluable for response. After 2 cycles of pembrolizumab-GVD, 34 patients had a CR (92%) and 3 had a partial response (PR; 8%). One patient with a CR was lost to follow-up. The 3 patients with a PR and 4 of those with a CR after the first 2 cycles received an additional 2 cycles of pembrolizumab-GVD. One patient converted from a PR to a CR, for an overall CR rate of 95%. Among the 7 patients who received an additional 2 cycles, one declined ASCT, and 6 underwent ASCT. Of the 35 patients who underwent ASCT, 11 received consolidation with brentuximab vedotin. No cases

of disease progression occurred after a median follow-up of 11.2 months following ASCT.

The treatment was well tolerated, with rash the most common AE (46%, n=17; Figure 3). Grade 3 AEs included rash (n=1), elevated levels of aspartate aminotransferase/alanine aminotransferase (AST/ALT, n=3), oral mucositis (n=2), and neutropenia (n=3). No treatment discontinuations occurred owing to AEs.

The investigators concluded that pembrolizumab-GVD is highly effective and well tolerated in patients with relapsed/refractory classical Hodgkin lymphoma. They aim to evaluate a transplant-free approach in which pembrolizumab-GVD is administered for 4 cycles, after which patients with a CR will continue treatment with 13 doses of pembrolizumab maintenance rather than proceed to ASCT.

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Consolidation With Nivolumab and Brentuximab Vedotin After Autologous Hematopoietic Cell Transplantation in Patients With High-Risk Hodgkin Lymphoma

Consolidation treatment with brentuximab vedotin plus nivolumab after autologous hematopoietic cell transplant (AHCT) is promising in patients with relapsed/refractory Hodgkin lymphoma, even those with high-risk factors, according to a presentation by Dr Alex F. Herrera.¹ The combination regimen was generally well tolerated, although more immune-related toxicity was observed in the post-transplant setting than is usually observed before transplant.

Since their advent, effective immunotherapies have been investigated in the post-transplant setting. In the phase 3 AETHERA trial, 16 cycles of brentuximab vedotin after AHCT improved 5-year PFS in patients with high-risk relapsed/refractory disease in comparison with placebo (59% vs 41%; hazard ratio [HR], 0.521; 95% CI, 0.379-0.717). However, the rate of peripheral neuropathy in this study was high, as was the rate of treatment discontinuation due to AEs.^{2,3} A phase 2 study of 30 patients with relapsed/refractory disease investigated the use of 8 doses of pembrolizumab after AHCT. The 19-month overall PFS rate was 81%. Therapy was generally well tolerated, with only 3 patients experiencing grade 3/4 AEs and 4 patients discontinuing treatment because of toxicity.⁴

On the basis of these data, the current study investigated the efficacy and safety of brentuximab vedotin plus nivolumab as consolidation after AHCT. Eligible adult patients had undergone AHCT and had at least one of the following risk factors: primary refractory disease, relapse within 1 year after completion of frontline therapy, extranodal disease or B symptoms at relapse, more than 1 salvage treatment before AHCT, and lack of a CR according to PET imaging after AHCT. Prior

exposure to brentuximab vedotin or a PD-1 inhibitor was allowed if disease had not progressed during treatment. Post-transplant consolidative radiation therapy was allowed if it had occurred before the initiation of study treatment. Patients with grade 2 or higher peripheral neuropathy and those without adequate organ function were excluded. Starting between days 30 and 75 after AHCT, patients received brentuximab vedotin at 1.8 mg/kg and nivolumab at 3 mg/kg every 21 days for a planned 8 cycles. Discontinuation of one drug did not preclude continuation of the other. Response and progression of disease were assessed according to the 2014 Lugano Classification. The primary endpoint was PFS. Secondary endpoints included overall survival and the response rate in patients without a CR at baseline.

The median age of the 59 enrolled patients was 30 years (range, 18-72), and 58% were male; 33% had primary refractory disease, 24% had B symptoms at relapse, 39% had extranodal disease at relapse, 25% had required 2 or more salvage regimens before transplant, and 19% were not in CR according to PET imaging at the time of transplant. In addition, 65% of the patients had 2 high-risk factors, and 24% had 3 or more high-risk factors. Previous treatment included brentuximab vedotin in 51%, a PD-1 inhibitor in 42%, and radiation in 24%.

Approximately 49% of the patients completed all 8 cycles of both agents, and 76% completed all 8 cycles of at least one of the agents. The overall 19-month PFS rate was 92% (95% CI, 79%-97%; Figure 4). The PFS rate varied with the number of high-risk factors (Figure 5). Of the 6 patients without a CR at baseline, 5 converted to CR during study treatment, whereas 1 continued to have a PR until disease

progression. The overall 19-month overall survival rate was 98% (95% CI, 88%-100%). One patient died of pneumonia that was not related to study treatment.

The most commonly reported AEs were peripheral sensory neuropathy (51%), neutropenia (42%), and fatigue (38%). The most common grade 3 or higher AEs were neutropenia (31%), pneumonitis (7%), and ALT elevation (5%). Immune-related AEs requiring systemic corticosteroids were recorded for 27% of the patients. The most frequent immune-related AEs included elevated liver function tests (14%), pneumonitis (14%), rash (12%), and hypothyroidism (7%).

The study investigators concluded that the administration of 8 cycles of brentuximab vedotin and nivolumab consolidation after AHCT in patients with high-risk, relapsed or refractory Hodgkin lymphoma is a promising approach. The combination was tolerable, although more immune-related toxicity occurred in the post-transplant setting than is usually observed before transplant. This combination warrants further study.

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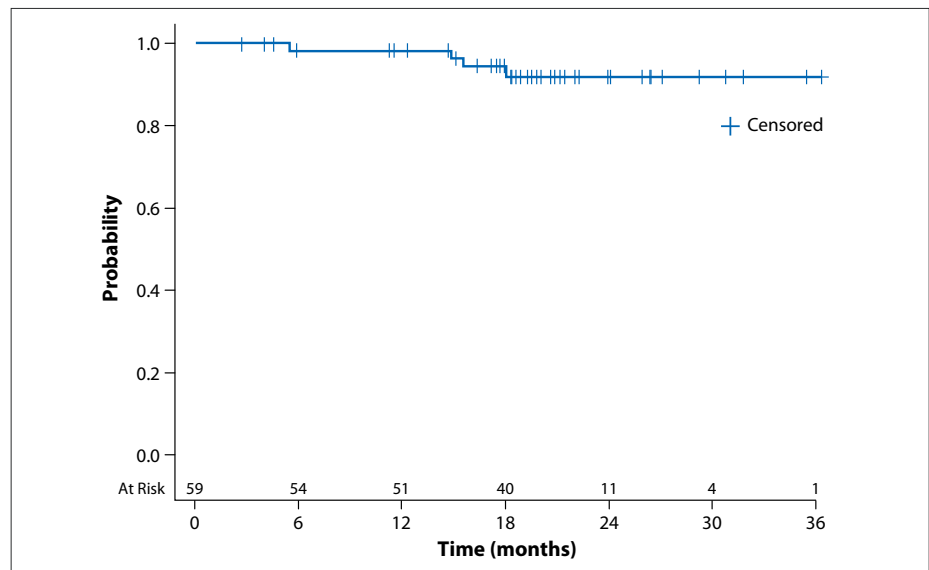
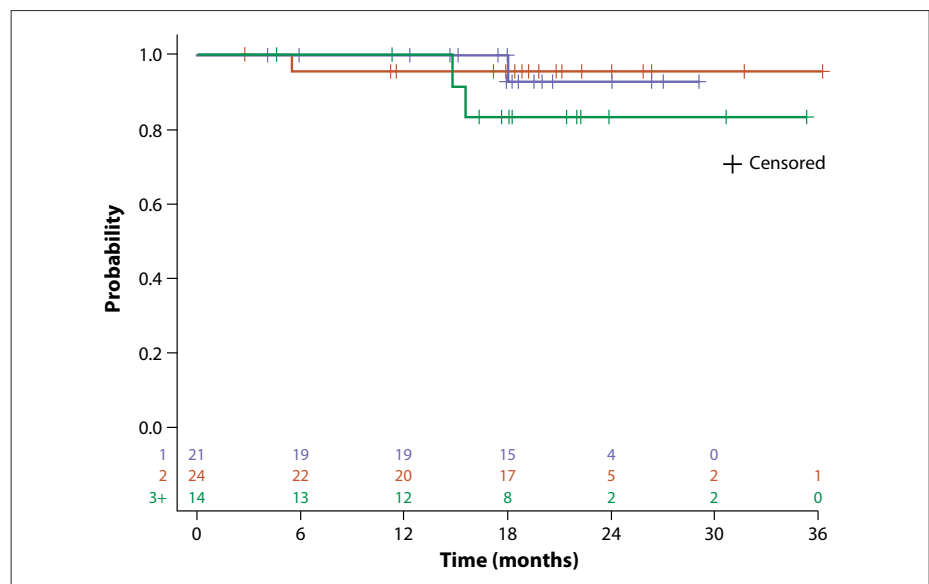


Figure 5. Progression-free survival according to the number of risk factors in a study of consolidation with nivolumab and brentuximab vedotin after autologous hematopoietic cell transplant in patients with high-risk Hodgkin lymphoma. Adapted from Herrera A et al. ASH abstract 472. *Blood*. 2020;136(suppl 1).¹



Preliminary Results of a Phase 2 Study of Camidanlumab Tesirine (Cami), a Novel Pyrrolobenzodiazepine-Based Antibody-Drug Conjugate, in Patients With Relapsed or Refractory Hodgkin Lymphoma

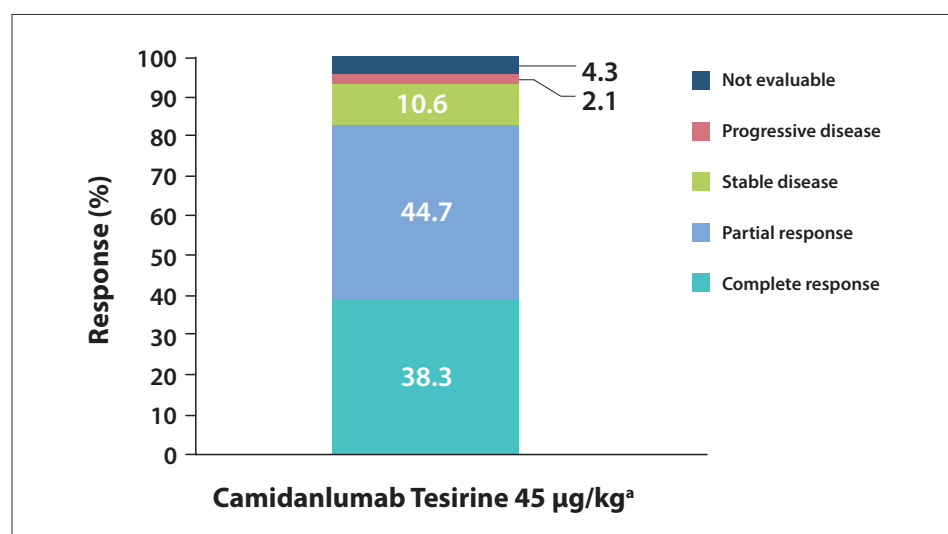
Camidanlumab tesirine is an investigational agent in which an anti-CD25 antibody is conjugated to a pyrrolobenzodiazepine dimer. The antibody portion binds to CD25-expressing tumor cells, and the dimer causes cell death via the formation of cytotoxic DNA cross-links that block cell division.¹ Data from

the phase 1 trial demonstrated an ORR of 86.5% (CR of 48.6%) with a dose of 45 μ g/kg in patients with relapsed/refractory classical Hodgkin lymphoma.² The agent had a generally acceptable safety profile, although Guillain-Barré syndrome developed in 5 of 77 patients.

An ongoing multicenter, open-

label, phase 2 trial is recruiting patients with relapsed/refractory classical Hodgkin lymphoma who have previously received 3 or more lines of treatment, including both brentuximab vedotin and a PD-1 inhibitor.³ The study is investigating the efficacy and safety of administering 2 cycles of camidanlumab tesirine at 45 μ g/kg,

Figure 6. Response in a phase 2 study evaluating camidanlumab tesirine in patients with relapsed/refractory classical Hodgkin lymphoma. ^aThe dose was 45 µg/kg for 2 cycles, and then 30 µg/kg for subsequent cycles. Adapted from Herrera A et al. ASH abstract 474. *Blood*. 2020;136(suppl 1).³



followed by camidanlumab tesirine at 30 µg/kg from cycle 3 onward, for up to 1 year. The primary objective is the ORR. Secondary endpoints include the CR rate, PR rate, and number of patients continuing to ASCT.

At the time of data cutoff on August 24, 2020, 51 patients were enrolled in the study. Their median age was 36 years (range, 20-74), and 71% were male. The patients received a median of 5 cycles of treatment (range, 1-11). The median number of prior therapies was 7, and 73% of the patients had previously undergone ASCT. Approximately 49% of the patients had disease that was refractory

to their most recent therapy.

The results were promising, with an ORR of 83%, a CR rate of 38%, and a PR rate of 45% (Figure 6). Stable disease was observed in 11% of patients, and 1 patient had progressive disease. Of the treated patients, 5 went on to receive a consolidated ASCT.

The most common treatment-emergent AEs included fatigue (51%), fever (39%), nausea (37%), and maculopapular rash (35.3%). The most common grade 3/4 treatment-emergent AEs were hypophosphatemia (12%) and increased gamma-glutamyltransferase. The most common treatment-emergent AEs thought to

be associated with the pyrrolbenzodiazepine dimer were skin reactions and nail disorders (72.5%) and liver function test abnormalities (33%). In 6 patients, treatment-emergent AEs led to a dose reduction or delay. In 7 patients, treatment-emergent AEs led to a discontinuation of treatment.

Enrollment was paused after investigators reported 2 cases of Guillain-Barré syndrome, in addition to other relevant severe neurologic toxicity. An independent review identified 1 case of grade 4 Guillain-Barré syndrome, 1 case of grade 2 Guillain-Barré syndrome, and 1 case of grade 2 radiculopathy. These numbers are comparable with those observed in the phase 1 study.¹ After the review, the enrollment pause was lifted.

ABSTRACT SUMMARY SWOG S1826: A Phase III, Randomized Study of Nivolumab Plus AVD or Brentuximab Vedotin Plus AVD in Patients With Newly Diagnosed Advanced-Stage Classical Hodgkin Lymphoma

SWOG S1826, a randomized phase 3 study of 6 cycles of nivolumab plus AVD or brentuximab vedotin plus AVD, is currently enrolling patients ages 12 years or older with newly diagnosed stage III/IV classical Hodgkin lymphoma (Abstract 2969). Patients with neuropathy higher than grade 2 at baseline are excluded. Those randomly assigned to brentuximab vedotin plus AVD are required to receive granulocyte colony-stimulating factor prophylaxis for neutropenia. The primary endpoint is PFS, and secondary endpoints include overall survival, event-free survival, end-of-treatment complete metabolic response rate, and safety. Another key secondary endpoint will be a comparison of patient-reported symptoms and health-related quality of life (overall, fatigue, neuropathy) in the 2 study arms. It is expected that a total of 940 eligible patients will be accrued over 4 years.

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Brentuximab Vedotin With Chemotherapy for Patients With Previously Untreated, Stage III/IV Classical Hodgkin Lymphoma: 5-Year Update of the ECHELON-1 Study

The phase 3 ECHELON-1 trial compared brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine (A+AVD) vs doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) in patients with newly diagnosed stage III/IV classical Hodgkin lymphoma. The modified 2-year PFS was 82.1% with A+AVD vs 77.2% with ABVD (HR, 0.77; 95% CI, 0.60 to 0.98; $P=.04$).¹ Follow-up studies revealed a 42-month PFS rate of 82.4% with A+AVD vs 76.2% with ABVD (HR, 0.697; 95% CI, 0.547-0.890). The PFS benefit with A+AVD vs ABVD was independent of interim PET scan status, disease stage, and baseline disease risk factor score. Dr David J. Straus presented updated efficacy and safety results from the ECHELON-1 study after a median follow-up of 55.6 months.²

ECHELON-1 randomly assigned patients to receive 6 cycles of A+AVD ($n=664$) or ABVD ($n=670$) IV on days 1 and 15 of a 28-day cycle. An interim PET scan after cycle 2 was required. Patients were assessed every 3 months

through month 36 and every 6 months thereafter. An exploratory analysis of PFS data was conducted with a cutoff date of May 18, 2020. The severity of peripheral neuropathy in patients with ongoing symptoms at the end of treatment was monitored. The investigators also assessed the rate of secondary malignancies and the incidence and outcomes of pregnancies among patients and partners.

The 5-year PFS rate was 82.2% (95% CI, 79.0%-85.0%) for the A+AVD arm and 75.3% (95% CI, 71.7%-78.5%) for the ABVD arm (HR, 0.691; 95% CI, 0.543-0.880; $P=.003$; Figure 7). The PFS benefits of A+AVD over ABVD were seen regardless of the interim PET scan status, number of risk factors (per the International Prognostic Factors Project on Advanced Hodgkin's Disease), baseline disease stage (III or IV), presence or absence of B symptoms at baseline, presence or absence of extranodal sites at baseline, and sex.

Among the patients with treatment-emergent peripheral neuropathy,

84% of those in the A+AVD arm and 85% of those in the ABVD arm who had symptoms at the end of treatment reported complete resolution or improvement of their symptoms after 5 years of follow-up. Of the 127 patients (29%) with ongoing peripheral neuropathy in the A+AVD arm, a maximum severity of grade 1, 2, 3, or 4 was seen in 17%, 9%, 3%, and 0.2%, respectively (Figure 8). Of the 59 patients (21%) with ongoing peripheral neuropathy in the ABVD arm, a maximum severity of grade 1, 2, 3, or 4 was seen in 14%, 6%, 1% and 0, respectively.

Secondary malignancies were reported in 2.9% of the A+AVD arm and 4.3% of the ABVD arm. A total of 150 pregnancies were reported among patients and their partners (89 in the A+AVD arm and 61 in the ABVD arm). The proportions of live births in the female patients and the partners of male patients were similar in the 2 arms.

The investigators concluded that A+AVD continues to demonstrate a

Figure 7. Progression-free survival at 5 years in the phase 3 ECHELON-1 study, which compared brentuximab vedotin plus AVD vs ABVD. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AVD, doxorubicin, vinblastine, and dacarbazine; HR, hazard ratio; PFS, progression-free survival. Adapted from Straus DJ et al. ASH abstract 2973. *Blood*. 2020;136(suppl 1).²

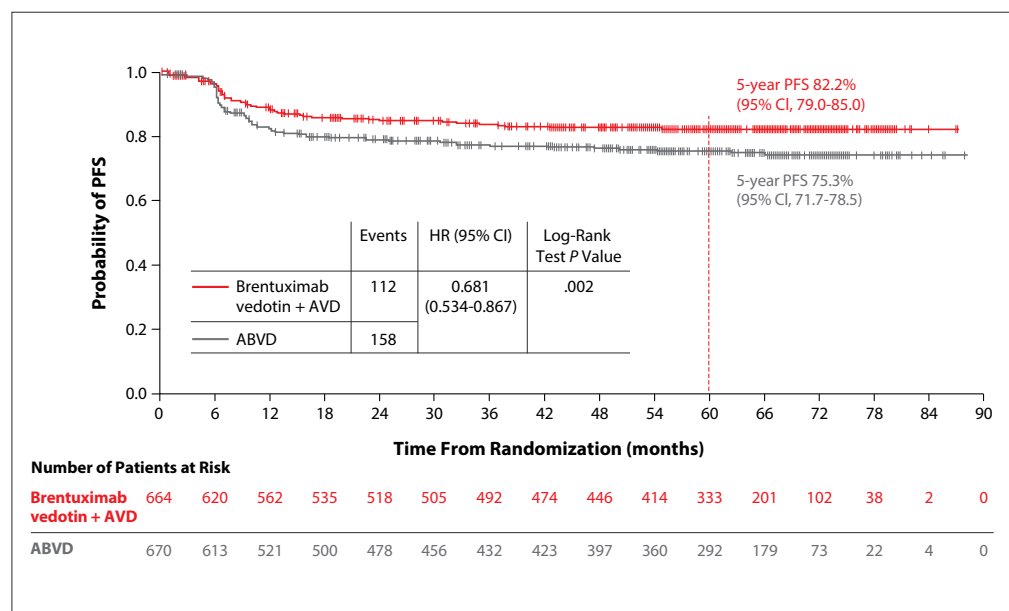
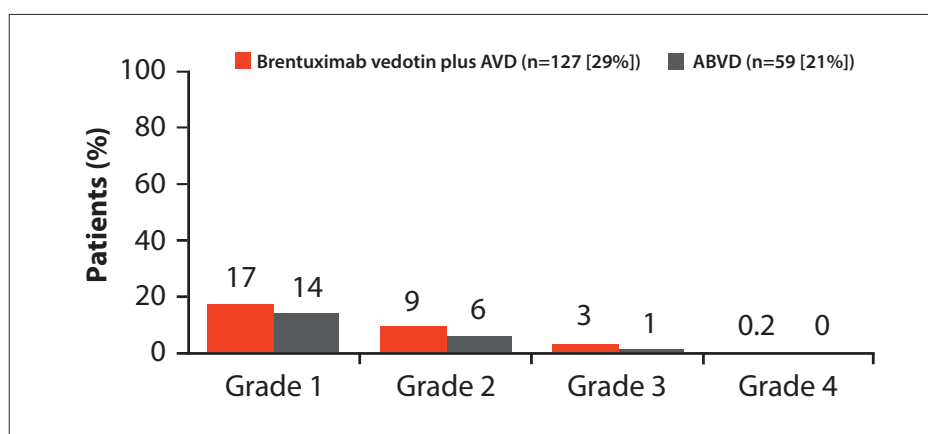


Figure 8. Rates of peripheral neuropathy in a 5-year analysis of the phase 3 ECHELON-1 study, which compared brentuximab vedotin plus AVD vs ABVD. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AVD, doxorubicin, vinblastine, and dacarbazine; Adapted from Straus DJ et al. ASH abstract 2973. *Blood*. 2020;136(suppl 1).²



robust and durable treatment benefit over ABVD after a 5-year follow-up that is independent of disease stage, risk factor score, and interim PET scan status. A+AVD may be considered as a preferred treatment option for patients

with previously untreated stage III or IV classical Hodgkin lymphoma.

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Everolimus Plus Itacitinib in Relapsed/Refractory Classical Hodgkin Lymphoma: Results of a Phase I/II Investigator Initiated Trial (EVITA Study)

The open-label, phase 1/2 EVITA study evaluated everolimus plus itacitinib in adult patients with an inadequate response to at least 2 prior lines of therapy and who underwent ASCT or who were ineligible for transplant.¹ Eligible patients also had an inadequate response to brentuximab vedotin and a PD-1 inhibitor or were ineligible for treatment with these agents. All patients received everolimus at 5 mg daily. The starting dose of itacitinib was 300 mg daily, with escalation to 400 mg daily or de-escalation to 200 mg daily, in a traditional 3+3 trial design. Treatment was planned for up to 24 cycles of 28 days each. All patients received *Pneumocystis jirovecii* pneumonia prophylaxis and, after an amendment, antiviral prophylaxis. Dose-limiting toxicities in the phase 1 portion were defined as any grade 3 or higher nonhematologic AE or selected grade 4 hematologic AEs that occurred

during the first cycle. The primary objective of the phase 2 portion was to evaluate efficacy (per the 2014 Lugano Classification). Enrollment began in

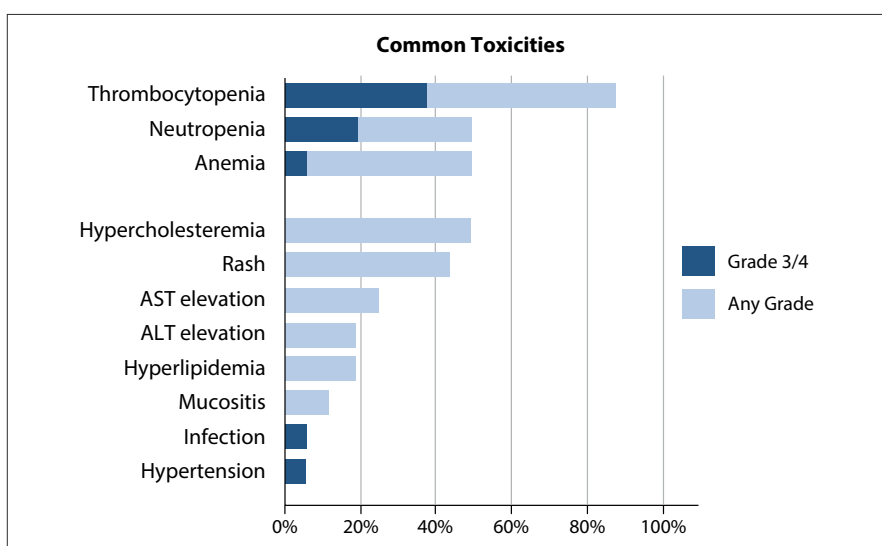
February 2019, and the data cutoff for this report was November 2020.

The median age of the evaluable patients (n=16) was 37 years (range,

ABSTRACT SUMMARY Effect of Pembrolizumab Monotherapy Versus Brentuximab Vedotin on Symptoms Associated With Health-Related Quality of Life in Relapsed/Refractory Classical Hodgkin Lymphoma in the Randomized, Phase 3, KEYNOTE-204 Study

This analysis of KEYNOTE-204 used the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 scale to evaluate patient-reported outcomes for fatigue, nausea/vomiting, pain, and B symptoms during treatment with pembrolizumab (n=146) or brentuximab vedotin (n=150; Abstract 374). Overall, measures of health-related quality of life improved with pembrolizumab and deteriorated with brentuximab vedotin. Improvements in mean scores for fatigue and pain during treatment with pembrolizumab were observed at week 6 and remained stable to week 48; scores with brentuximab vedotin remained stable to week 48. No differences were observed over time for pembrolizumab and brentuximab vedotin for mean nausea/vomiting scores. Among the patients with B symptoms at baseline, these symptoms resolved in 40 of 42 (95.2%) in the pembrolizumab group and 27 of 36 (75.0%) in the brentuximab vedotin group (P=.013).

Figure 9. Toxicities in a phase 1/2 trial of everolimus plus itacitinib in patients with relapsed/refractory classical Hodgkin lymphoma. ALT, alanine aminotransferase; AST, aspartate aminotransferase. Adapted from Svoboda J et al. ASH abstract 473. *Blood*. 2020;136(suppl 1).¹



22-68), and 69% were male. The median number of prior therapies was 5 (range, 4-9). All patients had previously received treatment with brentuximab vedotin, 94% had previously received PD-1 inhibitors, 69% had undergone ASCT, 19% had undergone allogeneic AHCT, and 13% had previously received anti-CD30 chimeric antigen receptor T cells.

No dose-limiting toxicities were identified during the first cycle in phase 1. The phase 2 doses were everolimus at 5 mg daily and itacitinib at 400 mg daily. Hematologic AEs were common, and included thrombocytopenia (88%), neutropenia (50%), and anemia (50%; Figure 9). Notable nonhematologic AEs that were generally attributed to everolimus included hypercholesterolemia (50%), acneiform

rash (44%), and mucositis dermatitis (12%). Grade 3/4 AEs, most of which were hematologic, included thrombocytopenia (38%), neutropenia (19%), anemia (7%), infection (7%), and hypertension (7%). There was one case of disseminated shingles requiring rehospitalization, but the patient recovered and resumed therapy. No treatment-related deaths occurred, and no patients discontinued treatment owing to AEs. Dose modification for hematologic toxicities was required for 6 patients (38%) after the first cycle.

The ORR in the combined phase 1/2 cohorts was 75% (CR rate, 12.5%), and 12.5% of the patients had stable disease. At a median follow-up of 10.7 months (range, 1.8-20.9), the median duration of response was 9.6 months (range, 1.6 to not determined). After

they had left the study, 2 patients died; one death was from progressive disease and the other from complications of allogeneic stem cell transplant.

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PET-Guided Strategy Improves the Safety of BEACOPP-Based Treatment in Advanced Hodgkin Lymphoma: Prolonged Follow-Up of the Lysa AHL 2011 Phase 3 Study

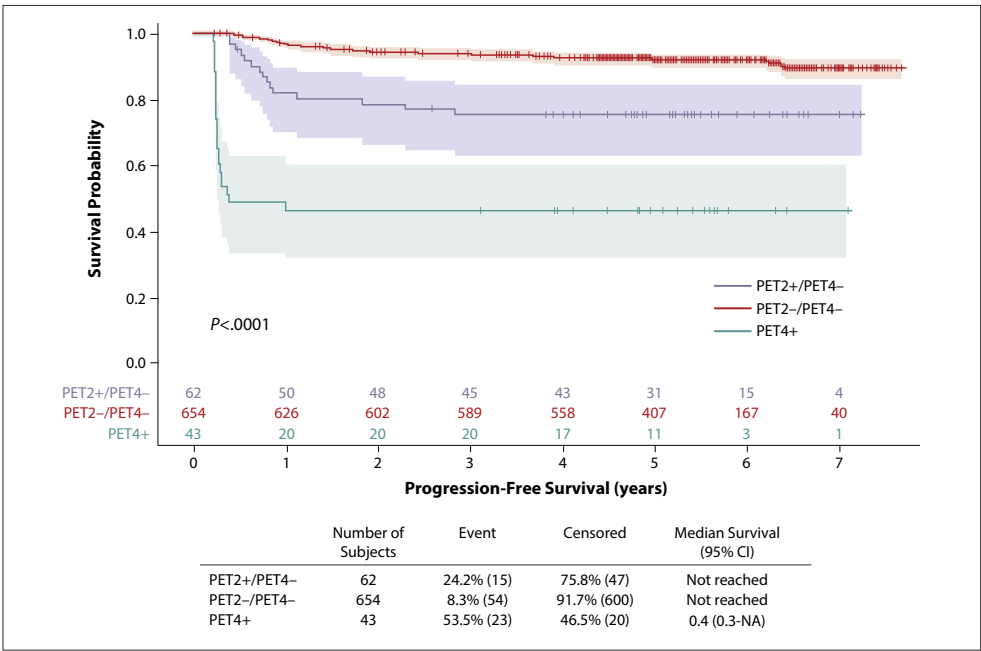
Previous results from the phase 3 AHL2011 study demonstrated that 84% of patients with previously untreated Hodgkin lymphoma with PET negativity after 2 cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (escalated

BEACOPP) could be switched to 4 cycles of ABVD, allowing an immediate reduction in treatment toxicity without loss of tumor control.¹ Dr Olivier Casasnovas reported the updated AHL2011 results.²

AHL2011 was a randomized phase 3 study (n=823) of patients with newly

diagnosed and untreated advanced Hodgkin lymphoma, excluding the nodular lymphocyte predominant subtype. The median age was 30 years (range, 16-60 years), and 63% were male. Escalated BEACOPP consisted of the following: bleomycin at 10 mg/m² and vincristine at 1.4 mg/m² IV on

Figure 10. Progression-free survival according to the PET-driven strategy in a follow-up analysis of the phase 3 AHL2011, which administered escalated BEACOPP to patients with newly diagnosed and untreated advanced Hodgkin lymphoma. BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; NA, not available; PET, position emission tomography. Adapted from Casasnovas O et al. ASH abstract 475. *Blood*. 2020;136(suppl 1).²



day 8, etoposide at 200 mg/m² IV on days 1 through 3, doxorubicin at 35 mg/m² and cyclophosphamide at 1250 mg/m² IV on day 1, procarbazine at 100 mg/m² orally on days 1 through 7, and prednisone at 40 mg/m² orally on days 1 through 14. Escalated BEACOPP was given every 21 days. ABVD consisted of the following: doxorubicin at 25 mg/m², bleomycin at 10 mg/m², vinblastine at 6 mg/m², and dacarbazine at 375 mg/m² IV on days 1 and 15. ABVD was given every 28 days.

All enrolled patients received 2 cycles of escalated BEACOPP followed by a PET assessment. In the standard treatment protocol, patients completed 4 additional cycles of escalated BEACOPP induction therapy irrespective of their PET findings. In the PET-driven protocol, patients with positive PET results received 4 additional cycles of escalated BEACOPP, whereas those with negative PET results were switched to ABVD. The primary endpoint of this noninferiority study was PFS, with secondary endpoints of overall survival, safety, and fertility.

After a median follow-up of 67.2 months, the 5-year PFS rates were similar in the PET-driven and

standard-protocol arms (PFS rates, 86.7% vs 87.5%; HR, 1.09; 95% CI, 0.75-1.58; *P*=.68). The overall survival rate was 97.7% in both arms (HR, 1.027; 95% CI, 0.5-2.1; *P*=.943). The rates of positive PET results after cycle 2 and cycle 4 did not differ significantly between the 2 arms. PET positivity after cycle 2 and cycle 4 was used to stratify patients, revealing 3 statistically significant different subsets for predicting PFS (*P*<.0001) and overall survival (*P*=.028). Patients who were PET-negative after cycles 2 and 4 (*n*=654) had a 5-year PFS rate of 92.3% and an overall survival rate of 98.2%, whereas those who were PET-positive after cycle 2 and PET-negative after cycle 4 (*n*=62) had a 5-year PFS rate of 75.4% and an overall survival rate of 93.5% (Figure 10). Those who were PET-positive after both cycle 2 and cycle 4 (*n*=43) had the worst outcomes, with a 5-year PFS rate of 46.5% and an overall survival rate of 91.9%.

The safety profile was tolerable in both arms. Statistically significant differences in the incidence of grade 3/4 AEs were noted for anemia (11% standard vs 2% PET-driven), leukopenia (85% vs 74%), thrombocytopenia (44% vs 15%), and sepsis (7% vs 3%).

Serious AEs were reported in 27% of patients in the standard arm and 17% of those in the PET-driven arm (*P*<.002). A secondary primary malignancy was reported in 3.2% vs 2.2%, respectively.

A fertility analysis included 145 women and 424 men ages 16 years to 45 years. In the fertility substudy, 32 female patients had primary ovarian insufficiency at years 5 to 6 (46% in the standard arm vs 15% in the PET-driven arm; HR, 0.20; 95% CI, 0.08-0.5; *P*<.001). Severe oligospermia at years 4 to 5 was seen in 50% of the male patients in the standard arm vs 93% of those in the PET-driven arm (*P*<.01). In the standard group, the total number of pregnancies was 37 among women and 7 among partners of male patients. The number of pregnancies was 39 and 22, respectively, in the PET-driven group. The PET-driven strategy provided a statistically significant improvement in male fertility (7 pregnancies vs 22 pregnancies; *P*=.004).

The study investigators concluded that the PET-driven induction strategy allowing 4 cycles of ABVD treatment in patients who are PET-negative after 2 cycles of escalated BEACOPP treatment is noninferior in comparison

with a standard protocol of 6 cycles of escalated BEACOPP induction treatment. The PET-driven treatment significantly reduces the incidence of some grade 3/4 hematologic AEs, and

also significantly decreases the risk for infertility in both sexes.

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Survival Outcomes for US and Canadian Patients Diagnosed With Hodgkin Lymphoma Before and After Brentuximab Vedotin Approval for Relapsed/Refractory Disease: A Retrospective Cohort Study

Insurance status affects the overall survival of patients with Hodgkin lymphoma treated in the United States.¹ Universal health care in Canada provides broad coverage, but approvals of new drugs can be delayed. Brentuximab vedotin was approved in the United States in 2011 and in Canada in 2014. The current retrospective cohort study compared overall survival in US and Canadian patients who received a diagnosis of classical Hodgkin lymphoma before and after brentuximab vedotin was approved in the United States. Dr Gwynivere A. Davies and colleagues hypothesized that existing differences in overall survival within the United States according to insurance type would widen after the approval, and that a survival gap would emerge between privately

insured US and Canadian patients owing to delayed approval in Canada.²

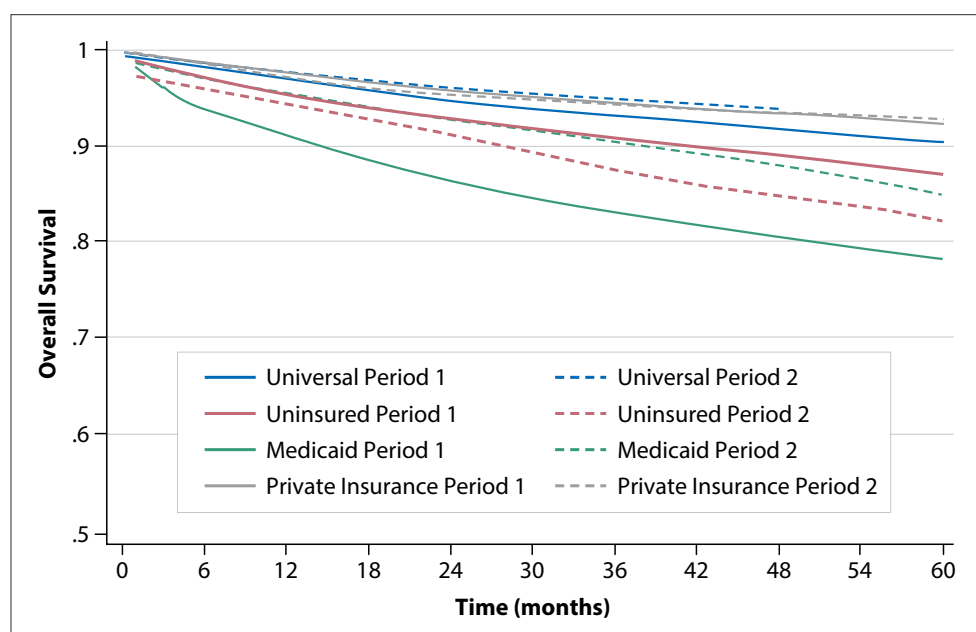
The study enrolled patients ages 16 to 64 years whose disease was diagnosed between 2007 and 2010 (period 1) or between 2011 and 2014 (period 2) and who were listed in the US Surveillance, Epidemiology, and End Results (SEER) Program or the Canadian Cancer Registry.

A total of 12,003 US and 4210 Canadian patients were included in the study. Patients in the United States demonstrated improved overall survival in period 2 vs period 1 in the adjusted analysis (adjusted HR, 0.80; 95% CI, 0.71-0.91; $P < .05$). Canadian patients showed significantly improved overall survival in period 2 vs period 1 in the unadjusted analysis (unadjusted HR, 0.72; 95% CI, 0.54-0.95;

$P < .05$), but not after adjustment. A comparison of all patients by country in the 2 periods showed no significant difference between overall survival in the US patients and the Canadian patients. Stratifying the US patients by insurance and comparing overall survival between period 2 and period 1 demonstrated stable overall survival for those with private insurance, significantly improved overall survival for those with Medicaid, and slightly worse overall survival for uninsured patients (a difference that did not reach statistical significance; Figure 11).

In the analysis of overall survival by insurance type, with use of universal insurance as the reference and after adjustment for time period, age, sex, and lymphoma subtype, an increased risk for death was found in

Figure 11. Overall survival according to insurance and time period among patients treated for Hodgkin lymphoma in the United States or Canada. Adapted from Davies G et al. ASH abstract 309. *Blood.* 2020;136(suppl 1).¹



uninsured patients (HR, 1.80; 95% CI, 1.46-2.20; $P<.0001$) and in Medicaid patients (HR, 2.36, 95% CI, 2.02-2.76; $P<.0001$). A reduced risk for death was reported among patients with private insurance (HR, 0.87, 95% CI, 0.77-1.00; $P=.044$). A 36-month comparison of overall survival in the 2 time periods according to insurance status identified a 7.4% improvement among Medicaid patients and a 2.4% improvement among universal insurance patients in period 2 vs period 1. No change between the 2 time periods was found in privately insured patients. A 4.1% decrease in survival was noted for uninsured patients.

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Hodgkin lymphoma before and after brentuximab vedotin approval for relapsed/refractory disease: a retrospective cohort study [ASH abstract 309]. *Blood*. 2020;136(suppl 1).

ABSTRACT SUMMARY Dose-Dense Brentuximab Vedotin Plus Ifosfamide, Carboplatin, and Etoposide (ICE) Is Highly Active for Second-Line Treatment in Relapsed/Refractory Classical Hodgkin Lymphoma: Final Results of a Phase I/II Study

A phase 1/2 trial examined the use of two 21-day cycles of dose-dense brentuximab vedotin and ICE chemotherapy in patients with first relapsed or primary refractory CD30+ classical Hodgkin lymphoma (Abstract 2964). PET was performed and stem cells collected after cycle 2. The primary endpoint was to determine the maximum tolerated dose and the CR rate after 2 cycles. Secondary endpoints included PFS, overall survival, stem cell collection, and molecular correlates. The median age of 45 enrolled patients was 31 years. At a median follow-up of 26.5 months, the ORR was 91% (CR rate, 74%), the 2-year PFS rate was 82%, and the 2-year overall survival rate was 98%. Grade 3/4 AEs included hypophosphatemia (11%), febrile neutropenia/sepsis (11%), elevated ALT (9%), hyperglycemia (7%), pulmonary embolism (4%), and neuropathy (2%). One patient died of multiple-organ failure.

Highlights in Hodgkin Lymphoma From the 62nd American Society of Hematology Annual Meeting and Exposition: Commentary

Andrew M. Evens, DO, MSc, FACP

Several studies presented at the 62nd American Society of Hematology (ASH) Annual Meeting and Exposition provided insight into the management of patients with Hodgkin lymphoma. New data were presented for targeted treatments such as brentuximab vedotin, pembrolizumab, and camidanlumab tesirine. I review here key data in Hodgkin lymphoma, as well as several select abstracts in B-cell non-Hodgkin lymphoma.

Brentuximab Vedotin

Dr David Straus provided results from a 5-year update of the ECHELON-1 study, which compared brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (AVD) vs doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) in patients with newly diagnosed, advanced-stage Hodgkin lymphoma.¹ Previous results from the

ECHELON-1 study were published in the *New England Journal of Medicine* and presented at earlier meetings.²⁻⁴

It is important for studies in Hodgkin lymphoma to continue to follow patients for at least 5 years. Among these patients, particularly those with advanced-stage disease, most relapses occur in the first 2 years. However, an additional 15% to 20% of patients may relapse through the 5-year mark.⁵ In addition, prognosis is worse among patients with an early positive positron emission tomography (PET) scan, but they represent a small minority of cases. Thus, most of the patients with advanced-stage Hodgkin lymphoma who relapse have a negative PET scan early in the disease course.

This long-term analysis of the ECHELON-1 study showed that the efficacy benefit reported with brentuximab vedotin at 2 years persisted

through years 3, 4, and 5.¹ At 5 years, progression-free survival was 82% with brentuximab vedotin plus AVD vs 75% with ABVD, for a hazard ratio of 0.68. Therefore, brentuximab vedotin plus AVD was associated with a 32% risk reduction in progression and death. The analysis also found that treatment-related toxicity improved with time. The investigators focused on peripheral neuropathy, which was increased in the brentuximab vedotin/AVD arm. Year after year, peripheral neuropathy improved or completely resolved among patients in both arms, including the brentuximab vedotin/AVD arm. By 5 years, neuropathy had either never occurred or completely resolved in 71% of patients treated with brentuximab vedotin, and neuropathy improved in 13%.

Dr Alex Herrera presented accrual data for the National Cancer

Institute's phase 3 randomized study of nivolumab plus AVD vs brentuximab vedotin plus AVD in patients with newly diagnosed advanced-stage Hodgkin lymphoma.⁶ The S1826 trial is a collaboration among SWOG, the Children's Oncology Group (COG), the Eastern Cooperative Oncology Group/American College of Radiology Imaging Network (ECOG/ACRIN), the Alliance for Clinical Trials in Oncology, and the Canadian Cancer Trials group. The trial is evaluating patients ages 12 years and older in North America. Because the study is not including bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) in a treatment arm, there is no upper age limit, allowing for more inclusive enrollment. Any study that includes BEACOPP must limit enrollment to patients younger than 60 years.

The standard-of-care arm in this study was drawn from the ECHELON-1 trial, and consists of brentuximab vedotin and AVD given for 6 cycles.² The experimental arm is nivolumab plus AVD. To date, the study has accrued approximately 240 patients. The planned enrollment is approximately 990 patients. I recommend that clinicians who treat patients with advanced-stage Hodgkin lymphoma contact the Clinical Trials of the Cancer Trials Support Unit about potentially opening this study at their institution. In addition, the trial design incorporates a host of important correlative studies, including quality of life, circulating tumor DNA, quantitative imaging, and economic analyses.

Dr Christopher Yasenchak presented results of our study evaluating brentuximab vedotin as monotherapy or in combination regimens as frontline treatment for older patients with Hodgkin lymphoma.⁷ In classical Hodgkin lymphoma, older patients (>60 years) have a significantly worse outcome compared with those who are younger. Before 2000, rates of survival at 3 and 5 years were only approximately 50% to 60% in older patients, compared with

90% in younger patients.

Researchers are increasingly using geriatric measurements to distinguish between older patients who are stronger, or "fit," from those who are frail, or "unfit." The study by Dr Yasenchak focused on older patients who were unfit. The study did not follow a formal geriatric assessment to define eligibility, but an overarching entry criteria permitted investigators to enroll patients who were not medically fit for multi-agent chemotherapy. This phase 2 study began treatment with brentuximab vedotin monotherapy, and then evaluated varied doublets by adding dacarbazine, bendamustine, or nivolumab (for a novel doublet). The patients' median age was 74 years.

The bendamustine arm closed early owing to multiple acute toxicities. Therefore, in older patients, the combination of bendamustine plus brentuximab vedotin is not recommended. For the other treatment arms, the overall response rates were high, above 90%. The rates of complete response ranged from 68% to 88%. The median duration of response ranged from 17 months to 23 months, so there was a drop-off from the high rates of complete remission. With that said, in most of the arms, there appeared to be a plateau at the 50% to 60% range for patients who achieved complete remission. This observation is important because these patients were newly diagnosed, and several had ended treatment with brentuximab vedotin monotherapy 3, 4, or even 5 years before the analysis. Even some patients treated with the doublets had stopped therapy years earlier. Although the rate of complete remissions might have been lower than hoped, it should be noted that the patients were older and unfit. In addition, the regimens were free of anthracycline. Based on this study, brentuximab vedotin as monotherapy or in combination with bendamustine or nivolumab are valid options for these unfit older Hodgkin lymphoma patients.

Dr Alex Herrera presented data from a phase 2 study of consolida-

tion with brentuximab vedotin and nivolumab after autologous stem cell transplant.⁸ In the AETHERA trial, which led the US Food and Drug Administration (FDA) to approve brentuximab vedotin for consolidation after an autologous transplant in relapsed/refractory classical Hodgkin lymphoma, the 5-year progression-free survival was approximately 60%.⁹ The benefit was even greater in patients with relapsed/refractory disease and multiple risk factors. The study by Dr Herrera aimed to improve upon this progression-free survival. The population was similar to that in AETHERA. Patients had at least 1 of the following characteristics: high-risk disease that was primary refractory or had relapsed within a year, extranodal involvement, B symptoms, lack of complete remission at transplant, and need for more than 1 salvage therapy. Treatment consisted of the doublet of brentuximab vedotin and nivolumab, given every 21 days for 8 cycles.

Overall, the treatment was well tolerated. Among 54 patients, the 19-month progression-free survival was 92%. These data are early, but highly encouraging. Longer follow-up is needed. An ongoing randomized study from ECOG is comparing the doublet of brentuximab vedotin and nivolumab with or without ipilimumab.¹⁰ It will be interesting to compare data from these studies. Multiple abstracts presented at the ASH meeting tested the strategy of integrating novel therapeutic agents earlier into the treatment armamentarium for patients with Hodgkin lymphoma.

Dr Pier Luigi Zinzani presented an interesting analysis of the randomized KEYNOTE-204 study, a phase 3 trial that compared brentuximab vedotin vs pembrolizumab in patients with relapsed or refractory classical Hodgkin lymphoma.¹¹ Patients were randomly assigned to treatment with brentuximab vedotin at the usual dose of 1.8 mg/kg every 3 weeks or pembrolizumab at 200 mg intravenously every weeks. The KEYNOTE-204 study met its primary endpoint, show-

ing that pembrolizumab had superior progression-free survival compared with brentuximab vedotin.¹²

The analysis by Dr Zinzani focused on health-related quality of life.¹¹ The investigators evaluated global health, as well as quality-of-life ratings for different functional domains (cognitive and emotional) and symptoms related to treatment, such as fatigue, nausea, vomiting, pain, and dyspnea. Overall, the health-related quality-of-life data favored pembrolizumab. This was not the case for all of the measures. Fatigue and pain showed an improvement with pembrolizumab over brentuximab vedotin, and this improvement remained stable over time. When considering treatments for patients with lymphoma, response rate and progression-free survival are important, but quality of life should also be considered.

Pembrolizumab Plus Gemcitabine, Vinorelbine, and Liposomal Doxorubicin

Dr Alison Moskowitz presented data from an important phase 2 study evaluating the tolerability and efficacy of pembrolizumab plus gemcitabine, vinorelbine, and liposomal doxorubicin in patients with relapsed/refractory Hodgkin lymphoma.¹³ The combination of gemcitabine, vinorelbine, and liposomal doxorubicin is a well-known active regimen.¹⁴ There are a host of different options in this setting. Most treatments have been studied in single-arm studies, phase 2 trials, or even retrospective analyses. There is a paucity of comparative research. As a general benchmark, chemotherapy has been associated with complete remission rates ranging from 40% to 50%. With novel regimens, such as sequential brentuximab vedotin used with ifosfamide, carboplatin and etoposide (ICE) or brentuximab vedotin combined with chemotherapy, the complete remission rates are higher, reaching 60% to 70%.^{2,15}

The study by Dr Moskowitz and colleagues aimed to find a tolerable treatment with as good, or better, rates

of complete remission that can be administered on an outpatient basis. Complete remission is the goal of first salvage therapy in relapsed Hodgkin lymphoma. It is known that patients who are in a complete remission at the time of transplant have superior outcomes.

In this phase 2 study, the combination of pembrolizumab plus gemcitabine, vinorelbine, and liposomal doxorubicin was effective.¹³ Among 37 evaluable patients, the complete remission rate was 95%, which is among the best ever reported. At a median follow-up of 11.2 months, there were no cases of progressive disease. Progression-free survival was therefore 100%. The treatment was well tolerated. Longer follow-up is needed, and the regimen must be evaluated in a larger number of patients. However, these data were striking.

Camidanlumab Tesirine

Dr Alex Herrera presented results from an open-label, multicenter phase 2 study of the antibody-drug conjugate camidanlumab tesirine (also known as cami) in patients with relapsed or refractory Hodgkin lymphoma.¹⁶ Camidanlumab tesirine is a CD25 antibody that is conjugated to a pyrrolizidine dimer as the cytotoxic agent. It is administered in a 30-minute intravenous infusion that is given every 3 weeks. Most of the patients in this trial had undergone an autologous stem cell transplant, and almost 100% of patients had experienced an inadequate response to previous treatment with brentuximab vedotin and programmed death 1 blockade. The overall response rate was an impressive 83%, with a complete remission rate of 38%. I am interested in seeing the data for the durability of this regimen. Overall, camidanlumab tesirine was well-tolerated. The most common grade 3 or higher treatment-emergent adverse events included low phosphate levels (12%), increased liver enzymes (6% to 10%), and rash (6%). A treatment-emergent adverse event led 14% of patients to withdraw from therapy.

Studies in Other Types of Lymphoma

Bispecific Antibodies

Several abstracts presented at the ASH meeting provided data for bispecific antibodies that target CD20 and CD3. These agents were highly efficacious in patients with relapsed/refractory B-cell lymphoma, in particular, diffuse large B-cell lymphoma and follicular lymphoma.¹⁷⁻¹⁹ They were associated with very high response rates, including complete remissions. Response rates were lower in patients who were resistant or refractory to CD19 chimeric antigen receptor (CAR) T-cell therapy, but any response rate with some degree of durability is an important finding in this group.

I am hopeful that at least one of the agents will be approved in 2021, which will add to the treatment armamentarium in B-cell lymphoma. It will also be interesting to see how these agents are sequenced with CAR T-cell therapy and other recently FDA-approved agents. Bispecific antibodies are associated with some toxicities, including immunosuppression. There is a slight increased risk of infections, some of which are cell-mediated. Cytokine release syndrome can occur, but the frequency and severity are far less than that seen in trials of CAR T-cell therapy.

Axicabtagene Ciloleucel

CD19 CAR T-cell therapy is currently approved by the FDA for the treatment of relapsed/refractory diffuse large B-cell lymphoma and mantle cell lymphoma. Dr Caron Jacobson presented results from the ZUMA-5 study, a phase 2 trial of axicabtagene ciloleucel in patients with relapsed/refractory indolent non-Hodgkin lymphoma.²⁰ The trial administered axicabtagene ciloleucel to 124 patients with follicular lymphoma and 22 patients with marginal cell lymphoma. Treatment was active in both groups. Among patients with follicular lymphoma, the overall response rate was 94%, including a complete remission rate of 80%. The duration of response appeared to be

markedly more durable in patients who were in a complete remission. Among all patients, at a median follow-up of 17.5 months, the median duration of response was not reached. According to the Kaplan-Meier curves at 24 months, the duration of response appeared to be just under 80% in patients with a complete remission. These data are impressive for this one-time treatment.

The side effects were similar to those seen in prior studies of CAR T-cell therapy. Grade 3/4 cytokine release syndrome was reported in 6% of patients with follicular lymphoma. Grade 3/4 neurologic events occurred in 15% of these patients. The study also included exploratory analyses of the association between CAR T-cell expansion and clinical outcomes, as well as a longitudinal profile of serum cytokines to identify any biomarkers of efficacy or neurologic events. These pharmacokinetic and pharmacodynamic analyses are early, but should provide important data. Before treatment, it would be helpful to have the ability to predict which patients are likely to garner the best benefit and to tolerate therapy well. Biomarker analyses will be important to study.

The Burkitt Lymphoma International Prognostic Index

My colleagues and I presented results from an analysis that aimed to develop a prognostic index for patients with follicular lymphoma.²¹ We examined data from more than 1000 patients across the world with newly diagnosed Burkitt lymphoma with the goal of creating a contemporary, validated prognostic index. The derivation cohort included 570 patients with Burkitt lymphoma. A validation cohort consisted of 457 patients throughout multiple countries in Europe, Canada, and Australia. We identified 4 dominant prognostic factors for progression-free survival and overall survival: ECOG performance status, age 40 years and older, levels of lactate dehydrogenase that were 3 times the upper limit of normal, and any central nervous system lymphoma involvement. The more of these fac-

tors the patient had, the worse the outcome. Among patients with zero factors in the derivation cohort, 3-year progression-free survival was 92%, and 3-year overall survival was 96%. Among patients with 2 or more of these factors, these survival rates were 53% and 59%, respectively. It is hoped that future prospective clinical studies will integrate these data. It may be possible for patients with favorable profiles to receive less-intense treatment, whether fewer drugs or fewer treatment cycles. Patients with a worse prognosis would need more novel therapeutics added to current treatment paradigms.

Disclosure

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