

A SPECIAL MEETING REVIEW EDITION

Highlights in Hodgkin Lymphoma From the 61st American Society of Hematology Annual Meeting

A Review of Selected Presentations From the 61st ASH Meeting

• December 7-10, 2019 • Orlando, Florida

Special Reporting on:

- Phase 2 Study of Frontline Brentuximab Vedotin Plus Nivolumab in Patients With Hodgkin Lymphoma Aged ≥ 60 Years
- 2-Year Follow-Up Results From the Phase 1-2 Study of Brentuximab Vedotin in Combination With Nivolumab in Patients With Relapsed or Refractory Hodgkin Lymphoma
- Brentuximab Vedotin With Chemotherapy for Stage 3/4 Classical Hodgkin Lymphoma: 4-Year Update of the ECHELON-1 Study
- Dose-Intensification in Early Unfavorable Hodgkin Lymphoma: Long-Term Follow-Up of the German Hodgkin Study Group (GHSG) HD14 Trial
- Brief Pembrolizumab Monotherapy Results in Complete and Near Complete Responses in the Majority of Untreated Patients With Classical Hodgkin Lymphoma: A Multicenter Phase 2 PET-Adapted Study of Sequential PEM and AVD
- Nivolumab and AVD for Early-Stage Unfavorable Hodgkin Lymphoma (NIVAHL)
- Reducing the Burden of Chemoradiotherapy With the Combination of Brentuximab Vedotin and Rituximab With Reduced-Toxicity Chemotherapy in Children, Adolescents, and Young Adults With Newly Diagnosed Hodgkin Lymphoma
- Combination of Oral Nanatinostat, a Novel Histone Deacetylase Inhibitor, and the Oral Anti-Viral, Valganciclovir, Is Active in Relapsed/Refractory Epstein-Barr Virus-Positive B-Cell, T-Cell, and Hodgkin Lymphoma: Interim Safety and Efficacy Results From a Phase 1b/2a Study

PLUS Meeting Abstract Summaries

With Expert Commentary by:

David J. Straus, MD

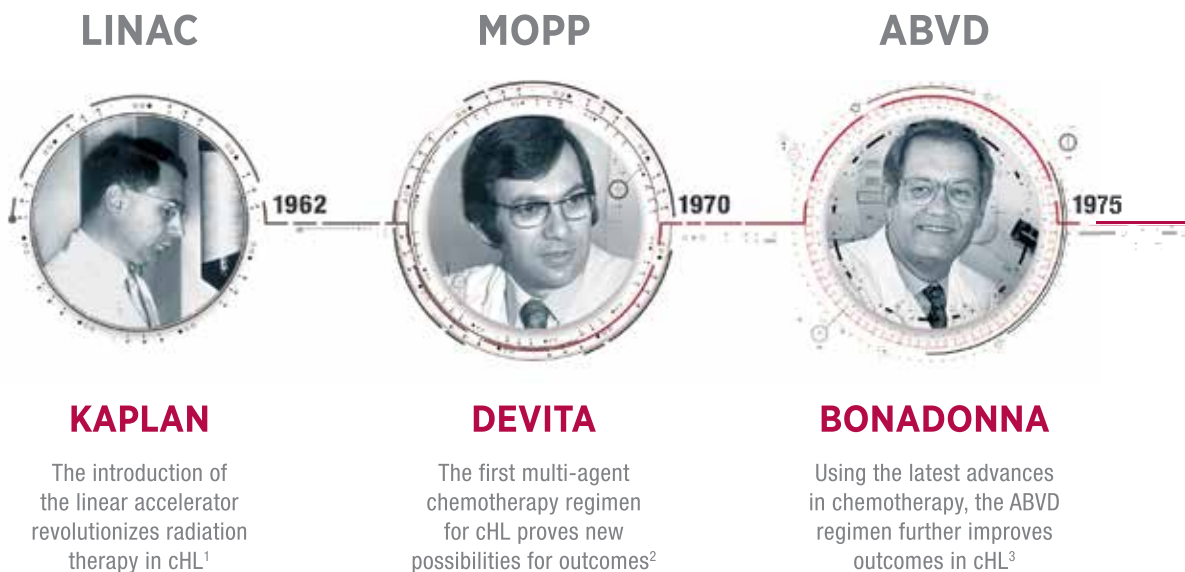
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ON THE WEB:
hematologyandoncology.net

ADCETRIS® (brentuximab vedotin) + AVD

THE FIRST FDA-APPROVED FRONTLINE REGIMEN IN OVER 40 YEARS

for Stage III/IV classical Hodgkin lymphoma (cHL)



NCCN
RECOMMENDATION

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Brentuximab vedotin (ADCETRIS®) + AVD now a Category 2A recommendation for frontline Stage III/IV cHL patients with no known neuropathy⁵

Indication

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

Important Safety Information

BOXED WARNING

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

Contraindication

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

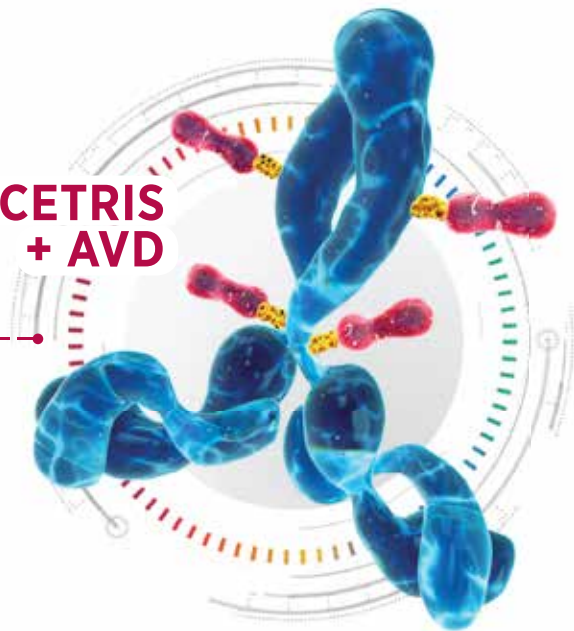
Warnings and Precautions

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

SUPERIOR EFFICACY vs ABVD

with no exposure to bleomycin

ADCETRIS
+ AVD



23%

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

Modified PFS per IRF: HR: 0.77 (95% CI: 0.60, 0.98); $P = 0.035$; primary endpoint; 24.6-month median follow-up time for both treatment arms⁴

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

Explore clinical data at

adcetrispro.com

ECHELON-1 TRIAL DESIGN: A randomized, open-label, multicenter trial assessing the efficacy and safety of ADCETRIS plus AVD [A+AVD] vs ABVD in 1334 adult patients with newly diagnosed Stage III/IV cHL. 664 patients were randomized to receive 1.2 mg/kg of ADCETRIS administered as an IV infusion over 30 minutes every 2 weeks for up to 12 doses + AVD, and 670 patients were randomized to 12 doses of ABVD. The primary endpoint was modified PFS per IRF; an event was defined as progression, death from any cause, or receipt of additional anticancer therapy for patients not in a complete response after completion of frontline therapy. The key secondary endpoint was OS.^{4,6}

Interim OS analysis

OS data are immature; an interim OS analysis did not demonstrate a significant difference between treatment arms.^{*4}

Most common adverse reactions in patients treated with A+AVD ($\geq 20\%$, with $\geq 5\%$ difference vs ABVD)

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

^{*}At the time of modified PFS analysis.

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

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

Important Safety Information, cont'd

- **Anaphylaxis and infusion reactions:** Infusion-related reactions (IRR), including anaphylaxis, have occurred with ADCETRIS® (brentuximab vedotin). Monitor patients during infusion. If an IRR occurs, interrupt the infusion and institute appropriate medical management. If anaphylaxis occurs, immediately and permanently discontinue the infusion and administer appropriate medical therapy. Premedicate patients with a prior IRR before subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.
- **Hematologic toxicities:** Fatal and serious cases of febrile neutropenia have been reported with ADCETRIS. Prolonged (≥ 1 week) severe neutropenia and Grade 3 or 4 thrombocytopenia or anemia can occur with ADCETRIS.
Administer G-CSF primary prophylaxis beginning with Cycle 1 for patients who receive ADCETRIS in combination with chemotherapy for previously untreated Stage III/IV cHL or previously untreated peripheral T-cell lymphomas.
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 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 ($\geq 20\%$ 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 following pages and full Prescribing Information at adcetrispro.com

References: 1. Kaplan HS. The radical radiotherapy of regionally localized Hodgkin's disease. *Radiology*. 1962;78:553-561. 2. DeVita VT Jr, Serpick AA, Carbone PP. Combination chemotherapy in the treatment of advanced Hodgkin's disease. *Ann Intern Med*. 1970;73:881-895. 3. Bonadonna G, Zucali R, Monfardini S, De Lena M, Uslenghi C. Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. *Cancer*. 1975;36(1):252-259. 4. ADCETRIS [Prescribing Information], Bothell, WA: Seattle Genetics, Inc. October 2019. 5. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hodgkin Lymphoma (V.1.2019). © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed April 24, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. 6. 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 ≥Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. Due to higher MMAE exposure, ≥Grade 3 adverse reactions may be more frequent in patients with severe renal impairment compared to patients with normal renal function. Avoid the use of ADCETRIS in patients with severe renal impairment (CrCL <30 mL/min).

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

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

5.8 Hepatotoxicity

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

5.9 Progressive Multifocal Leukoencephalopathy

Fatal cases of JC virus infection resulting in PML have been reported in ADCETRIS-treated patients. First onset of symptoms occurred at various times from initiation of ADCETRIS therapy, with some cases occurring within 3 months of initial exposure. In addition to ADCETRIS therapy, other possible contributory factors include prior therapies and underlying disease that may cause immunosuppression. Consider the diagnosis of PML in any patient presenting with new-onset signs and symptoms of central nervous system abnormalities. Hold ADCETRIS dosing for any suspected case of PML and discontinue ADCETRIS dosing if a diagnosis of PML is confirmed.

5.10 Pulmonary Toxicity

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

5.11 Serious Dermatologic Reactions

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

5.12 Gastrointestinal Complications

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

5.13 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: noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and ARDS (some with fatal outcomes).

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

6.3 Immunogenicity

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

Patients with cHL and 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 adacetrispro.com



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Phase 2 Study of Frontline Brentuximab Vedotin Plus Nivolumab in Patients With Hodgkin Lymphoma Aged ≥ 60 Years

The combination of brentuximab vedotin with nivolumab was active and well tolerated in an ongoing phase 2 trial of patients ages 60 years or older with newly diagnosed Hodgkin lymphoma.¹ Dr Christopher A. Yasenchak and colleagues presented results from the trial. Hodgkin lymphoma has a bimodal age distribution in some populations, with incidence often peaking in the third and sixth decades of life.² Diagnoses of Hodgkin lymphoma among patients ages 60 years or older represent approximately 20% of all cases, although the rate varies across reports.¹⁻³ Outcomes in older patients with Hodgkin lymphoma are inferior to those in younger patients, with some survival differences attributable to causes other than the disease.⁴ Older patients may be unable to tolerate some of the newer treatments.⁵ In

many elderly patients, fatalities result from lymphoma that is insufficiently controlled.⁵

In 2018, a phase 1/2 study evaluated brentuximab vedotin and nivolumab in 30 younger patients (median age, 31.5 years) with relapsed/refractory Hodgkin lymphoma.⁶ The regimen was well tolerated and led to a complete response (CR) rate of 80%.

The open-label, phase 2 study in older patients administered brentuximab vedotin at 1.8 mg/kg and nivolumab at 3 mg/kg by intravenous infusion at 3-week intervals for up to 16 cycles.^{1,7} The patients enrolled in the study were ineligible for conventional combination chemotherapy or had declined treatment. Other eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) score of 2 or less, creatinine clearance of at

least 30 mL/min, diffusing capacity greater than 50%, measurable disease of at least 1.5 cm, and lack of autoimmune disease. The median age of the patients was 72.0 years (range, 60-88 years), and 76% of them had presented with stage 3 or 4 disease. Nearly half of patients (48%) had bulky disease.

The primary endpoint of the study was the overall response rate (ORR). Additional endpoints included safety, CR rate, duration of response, overall survival, and progression-free survival (PFS). Computed tomography (CT) and positron emission tomography (PET) were used to evaluate responses. A CT-only evaluation was performed at cycle 2, and CT and PET evaluations were conducted at later points throughout the study.

At the time of the report, among the 21 patients who received therapy,

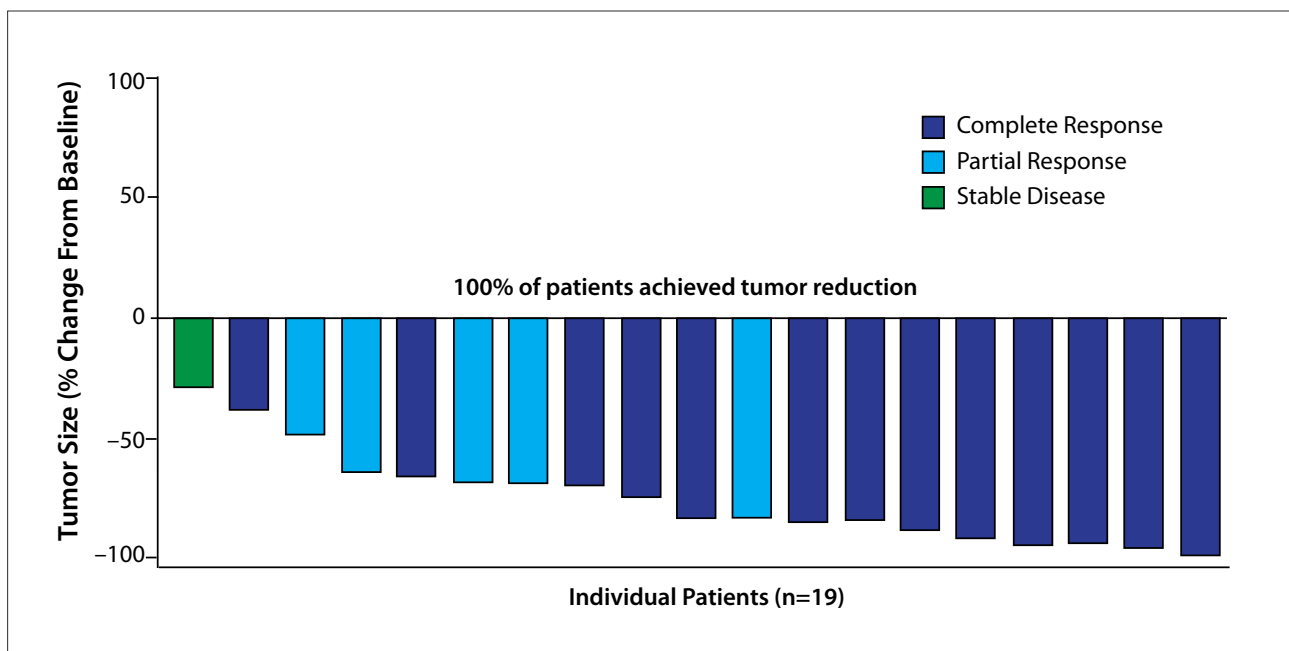


Figure 1. Maximum percent reduction from baseline in the sum of diameters of target lesions in a phase 2 trial of frontline brentuximab vedotin plus nivolumab in older patients with Hodgkin lymphoma. Data are shown for patients evaluable for efficacy. Adapted from Yasenchak CA et al. ASH abstract 237. *Blood*. 2019;134(suppl 1).¹

4 remained on treatment, 9 were in long-term follow-up, 2 withdrew consent, 2 died, and 4 discontinued treatment but had not yet entered into the long-term follow-up window. Of the 17 patients who discontinued treatment, 6 completed planned therapy, 3 had progressive disease, 4 discontinued after an adverse event (AE), and 4 chose to discontinue. No treatment discontinuations owing to AEs were considered treatment-related. The median number of treatment cycles of brentuximab vedotin or nivolumab was 10 (range, 1-16) per patient. Patients received a median of 9 cycles (range, 1-16) of brentuximab vedotin and 9 cycles (range, 1-16) of nivolumab.

At the time of the study report, the median duration of follow-up was 6.8 months.¹ The ORR in 19 evaluable patients was 95%, with 68% of patients achieving a CR. No patients showed signs of disease progression, and 5% had stable disease. Tumor size decreased in 100% of the patients (Figure 1). The median duration of

response was not reached (Figure 2).

The most common treatment-related AE was peripheral neuropathy, which occurred in 52% of patients.¹ Grade 3 or higher treatment-related AEs were reported in 57% of patients. A grade 3 or higher increase in lipase was reported in 24%. Treatment-related grade 3 or higher peripheral neuropathy and sensory neuropathy each occurred in 14% of patients. Infusion-related reactions of any grade were reported in 29% of patients; all cases were grade 2 or lower. There was 1 treatment-related serious AE—pyrexia—which was considered related to both brentuximab vedotin and nivolumab.

The study investigators concluded that the combination of brentuximab vedotin and nivolumab is an active and well-tolerated frontline regimen for patients ages 60 years or older who are ineligible for or have declined conventional therapy.¹ The combination of brentuximab vedotin and nivolumab continues to be evaluated in this study.

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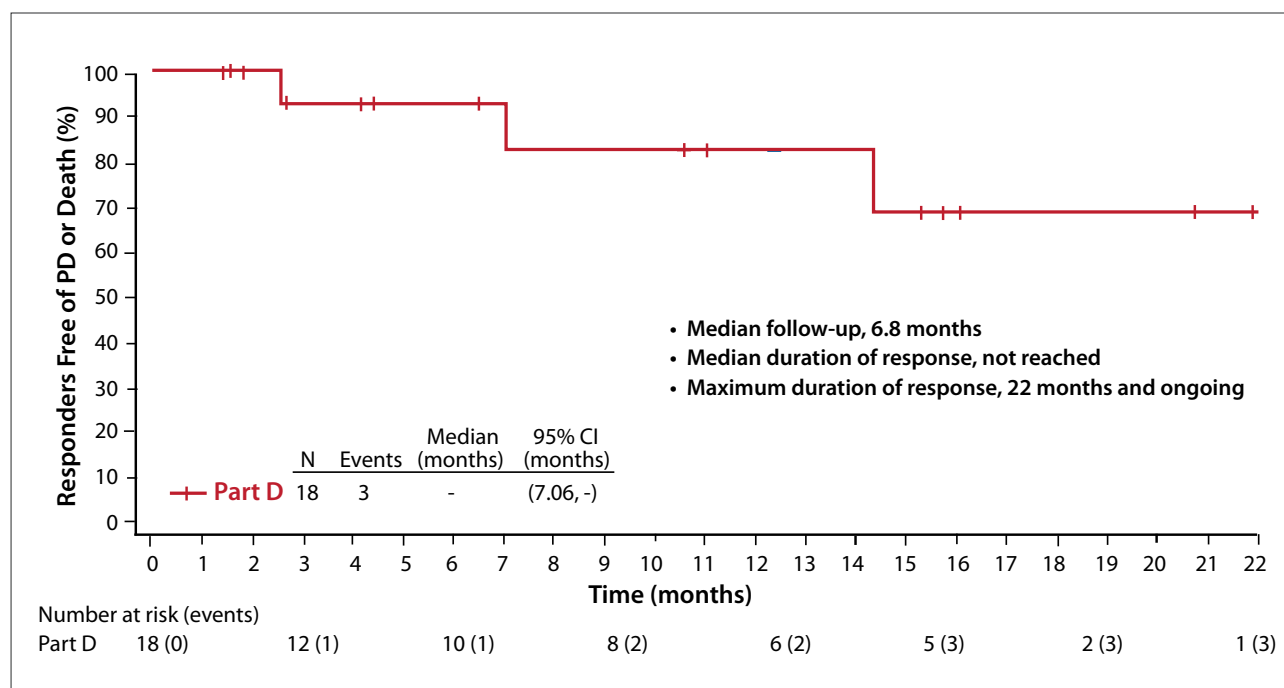


Figure 2. Duration of response in a phase 2 trial of frontline brentuximab vedotin plus nivolumab in older patients with Hodgkin lymphoma. PD, progressive disease. Adapted from Yasenchak CA et al. ASH abstract 237. *Blood*. 2019;134(suppl 1).¹

2-Year Follow-Up Results From the Phase 1-2 Study of Brentuximab Vedotin in Combination With Nivolumab in Patients With Relapsed or Refractory Hodgkin Lymphoma

Two-year follow-up results of a single-arm phase 1/2 study showed that the combination of brentuximab vedotin plus nivolumab was well tolerated and yielded high CR rates in patients with relapsed/refractory classical Hodgkin lymphoma.¹ An interim analysis of this study previously demonstrated that the combination of brentuximab vedotin and nivolumab, which can restore antitumor immunity to activated T cells, is well tolerated and effective.² The new analysis included long-term follow-up data for the combination administered in staggered and concurrent dosing schedules. In addition, the investigators tested whether innate and adaptive immune response biomarkers in the peripheral blood correlated to clinical response.

All patients had classical Hodgkin lymphoma that was refractory to or had relapsed during frontline chemotherapy. For the staggered dosing regimen, patients received up to 4 cycles of the following: brentuximab vedotin (1.8 mg/kg) on day 1 and nivolumab (3.0 mg/kg) on day 8 of cycle 1, followed by brentuximab vedotin plus nivolumab on day 1 of cycles 2 through 4. The duration of each cycle was 21 days. For the concurrent dosing regimen, patients received both drugs on day 1 of all 4 cycles. Response was assessed by CT after 2 cycles and by PET after 4 cycles, after which patients could undergo autologous stem cell transplant (ASCT).

The primary endpoint was assessment of the safety of the drug combination and the CR rate according to

the Lugano 2014 criteria. Secondary endpoints included ORR, duration of response, PFS rate, and biomarker analysis.

The trial enrolled 93 patients; however, 2 patients did not receive treatment.¹ Most patients (n=51) were female. The median age was 34 years (range, 18-69 years). Primary refractory disease was reported in 42% of patients, and 26% had extranodal disease. In 30% of patients, the disease had relapsed within 1 year of frontline therapy. At the time of the study report, all patients had ended treatment and completed the 100-day safety reporting period.

Data for the 2 treatment regimens were presented as combined results because their overall efficacy and tolerability were similar.¹ Most

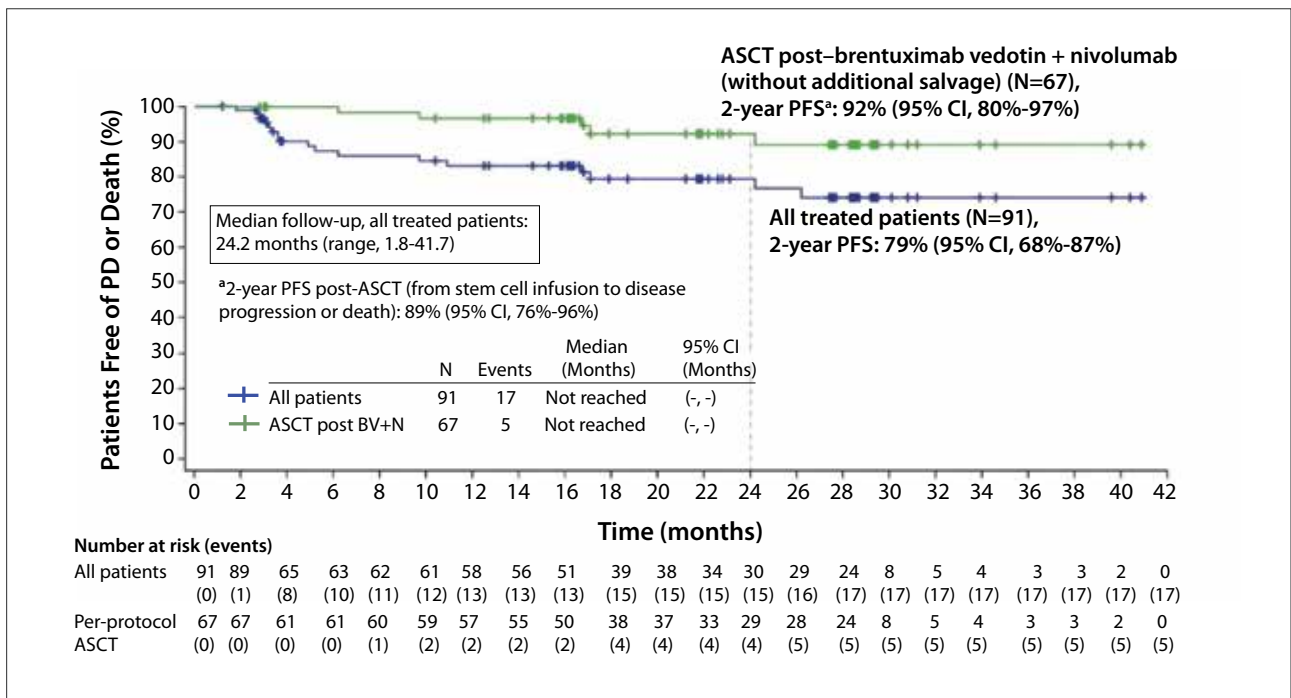


Figure 3. PFS in a phase 1/2 study of brentuximab vedotin in combination with nivolumab in patients with relapsed/refractory Hodgkin lymphoma. ASCT, autologous stem cell transplant; BV, brentuximab vedotin; N, nivolumab; PD, progressive disease; PFS, progression-free survival. Adapted from Moskowitz AJ et al. ASH abstract 238. *Blood*. 2019;134(suppl 1).¹

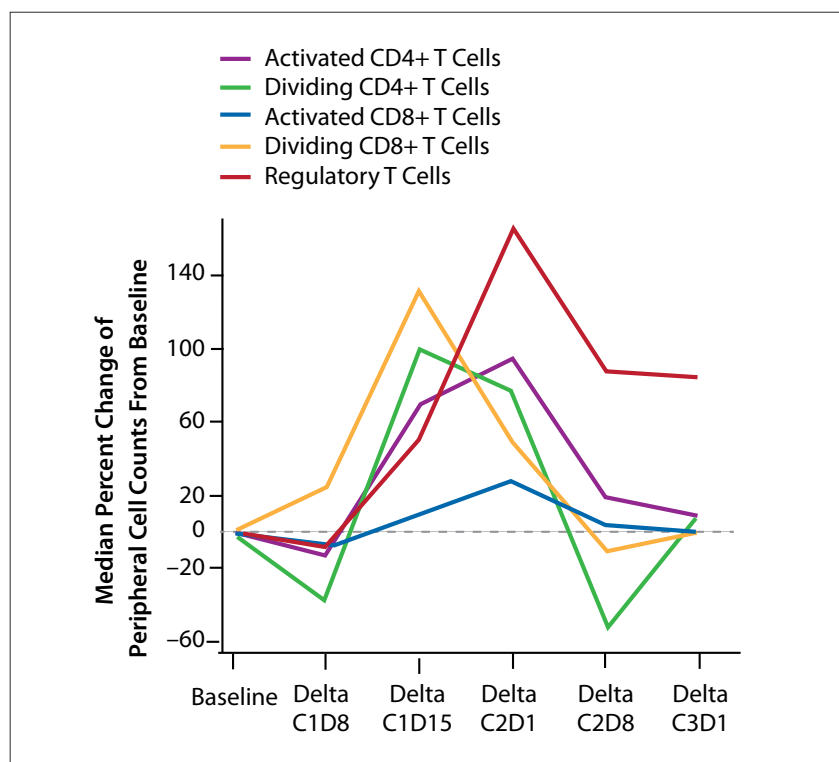


Figure 4. Follow-up analysis of T-cell signatures after treatment in a phase 1/2 study of brentuximab vedotin in combination with nivolumab in patients with relapsed/refractory Hodgkin lymphoma. C, cycle; D, day. Adapted from Moskowitz AJ et al. ASH abstract 238. *Blood*. 2019;134(suppl 1).¹

patients (92%) completed all 4 cycles of brentuximab vedotin plus nivolumab. Among the 91 treated patients, the ORR was 85%, with a CR of 67%. Most patients (74%) underwent ASCT after the combination treatment.¹ Additional salvage therapy was needed by approximately 25% of patients: 7 with progressive disease, 6 with a partial response, 5 with stable disease, and 4 with a CR. Of those patients, 77% also went on to ASCT. At a median follow-up of 24.2 months (range, 1.8-41.7 months), the estimated 2-year PFS rate was 79% (95% CI, 68%-87%) for all treated patients and 92% (95% CI, 80%-97%; Figure 3) for patients who underwent ASCT after the combination treatment, without salvage therapy. The 2-year estimated overall survival rate for all treated patients was 94% (95% CI, 85%-97%).

Both treatment schedules led to increased levels of activated and dividing CD4-positive T cells, regulatory T cells, and circulating plasmablasts (Figure 4). The increase was slightly higher in the concurrent dosing arm. These findings suggest, as expected,

an enhancement of the anti-tumor immune response. However, the magnitudes of the changes were not associated with clinical response.

The investigators performed RNA sequencing analysis of 50 baseline tumor samples for 132 different markers of immune cells, inflammatory response, and the tumor microenvironment. The combination treatment led to significant changes in the levels of cytokines and chemokines, including increased levels of interleukin (IL)-18, interferon gamma-induced protein-10, interferon-inducible T-cell alpha chemoattractant, and CD30, as well as decreased levels of thymus and activation-regulated chemokine (TARC), IL-2 receptor alpha, and IL-6. Expression of CD30 was significantly higher among responders vs nonresponders. The other changes did not correlate with clinical response.

No unexpected AEs occurred, and most AEs were grade 1 to 2.¹ The most common AEs were nausea (52%), infusion-related reactions (43%), and fatigue (40%). Serious AEs occurred in 15% of patients; they included

pneumonia, pneumonitis, and pyrexia (each in 2 patients) and Guillain-Barré syndrome (in 1 patient). Treatment was discontinued in 5 patients; the reasons were peripheral neuropathy (grade 3), elevated gamma-glutamyl transferase, progressive disease, investigator decision, and patient decision.

The authors concluded that the results of the study support further investigation of brentuximab vedotin plus nivolumab as initial salvage therapy in relapsed/refractory classical Hodgkin lymphoma.¹ The analysis of blood biomarkers may link baseline levels of CD30-positive immune cells and the inflammatory state with the activity of this combination treatment.

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Brentuximab Vedotin With Chemotherapy for Stage 3/4 Classical Hodgkin Lymphoma: 4-Year Update of the ECHELON-1 Study

In a 4-year update of the phase 3 ECHELON-1 trial (A Frontline Therapy Trial in Participants With Advanced Classical Hodgkin Lymphoma), treatment with brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (AVD) continued to improve PFS in patients with classical Hodgkin lymphoma, regardless of PET2 status and without the need for treatment intensification, as compared with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD).¹ The ECHELON-1 trial compared brentuximab vedotin plus AVD vs ABVD in patients with treatment-naïve stage III or IV classical Hodgkin lymphoma.² In the primary analysis, the 2-year modified PFS rate was 82.1% in the brentuximab vedotin/AVD arm vs 77.2% in the ABVD arm (hazard ratio [HR], 0.77; 95% CI, 0.60-0.98; $P=.035$).⁵

The 4-year post-hoc exploratory analysis evaluated PFS per investigator assessment among the intention-to-treat population (N=1334).¹ Sub-

group analyses included PET2 status, age, stage, and prognostic risk scores. Among the 664 patients treated with brentuximab vedotin plus AVD, 57% were male; 59% of the 690 patients in the ABVD arm were male. The patients' median age was 35 years (range, 18-82) in the brentuximab vedotin/AVD arm and 37 years (range, 18-83) in the ABVD arm. B symptoms were present in 60% vs 57%, respectively. Stage IV disease was reported in 64% vs 63%, respectively, with stage III disease in the remaining patients.

At a median follow-up of 48.4 months, the 4-year PFS rate was 81.7% with brentuximab vedotin plus AVD vs 75.1% with ABVD (HR, 0.691; 95% CI, 0.542-0.881; $P=.003$; Figure 5).¹ Treatment with brentuximab vedotin plus AVD decreased the risk for disease progression or death by 31%. The improvement in the PFS rate with brentuximab vedotin plus AVD was observed in most of the pre-specified subgroups, including those based on age, prognostic score, and

disease stage, although the confidence intervals of the 2 arms overlapped.

At the primary analysis, peripheral neuropathy was reported in 67% of patients receiving brentuximab vedotin plus AVD and 43% of those receiving ABVD.⁵ At 4-year follow-up, peripheral neuropathy had improved or resolved in 83% and 84% of these patients, respectively.¹ Peripheral neuropathy had resolved completely in 68% vs 76% by 4 years. Ongoing peripheral neuropathy was reported in 21% of patients (n=142) in the brentuximab vedotin/AVD arm and 10% of patients (n=69) in the ABVD arm. Most cases of peripheral neuropathy were grade 1 or 2.

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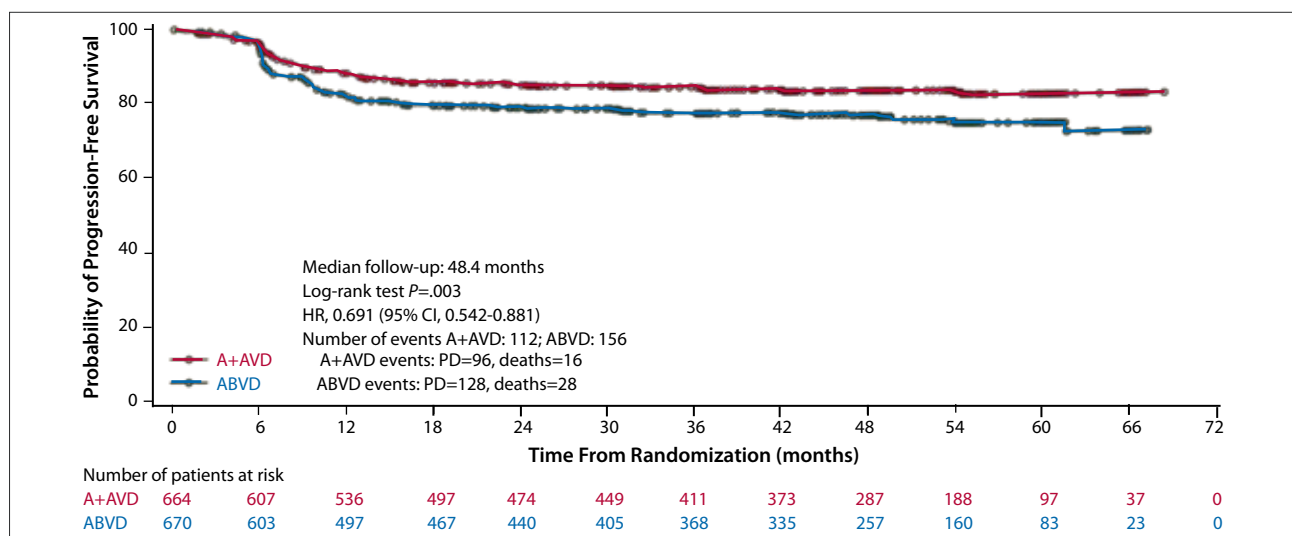


Figure 5. Follow-up analysis of progression-free survival per investigator assessment in the intention-to-treat population of the ECHELON-1 trial, which compared brentuximab vedotin plus AVD vs ABVD in patients with treatment-naïve stage III or IV classical Hodgkin lymphoma. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AVD, doxorubicin, vinblastine, and dacarbazine; ECHELON-1, A Frontline Therapy Trial in Participants With Advanced Classical Hodgkin Lymphoma; PD, progressive disease. Adapted from Bartlett NL et al. ASH abstract 4026. *Blood*. 2019;134(suppl 1).¹

Dose-Intensification in Early Unfavorable Hodgkin Lymphoma: Long-Term Follow-Up of the German Hodgkin Study Group (GHSG) HD14 Trial

The German Hodgkin Study Group (GHSG) HD14 trial evaluated whether an intensified 2+2 regimen, consisting of 2 cycles of escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) followed by 2 cycles of ABVD, would improve long-term survival vs standard of care among patients with early unfavorable Hodgkin lymphoma.^{1,2} The trial enrolled patients between January 2003 and July 2008. Patients were ages 60 years or younger. They were randomly assigned to treatment with 4 cycles of ABVD (ABVD × 4) or the dose-intensified 2+2 regimen. All patients received involved-field radiotherapy at a dose of 30 Gy.

At the initial 5-year report of the trial, the PFS rate was 95.3% in the 2+2 arm vs 89.3% in the ABVD × 4 arm, a statistically significant improve-

ment.² No significant differences were observed in overall survival or treatment-related mortality. Additionally, no differences were observed between the treatment arms in second primary malignancies or in rates of infertility among female patients ages 45 years or younger in ongoing remission.³

In a survey administered to survivors of Hodgkin lymphoma, including patients who participated in HD14, the respondents reported no difference between the chemotherapy burden of the dose-intensified 2+2 regimen and that of the prior standard-of-care ABVD × 4 regimen.⁴ Additionally, according to the survey results, the potential for second malignancies and the possibility of relapse were considered critical potential burdens. Most patients regarded cure as the primary goal of therapy.

This long-term follow-up of the HD14 trial aimed to address concerns

about potential long-term toxicities and the lack of difference in overall survival.¹ According to a preplanned interim analysis conducted in 2008, outcomes in the ABVD × 4 arm were significantly inferior, so enrollment into that treatment arm was discontinued.² This long-term follow-up included 1112 patients treated with the 2+2 regimen and 777 patients treated with the ABVD × 4 regimen.¹

At a median follow-up of 97 months, patients treated with the 2+2 regimen had significantly fewer cases of disease recurrence (HR, 0.0521; 95% CI, 0.386-0.704; $P < .0001$).¹ The 10-year PFS rate of the 2+2 arm was superior, at 91.2% (95% CI, 89.0%-93.4%), vs 85.6% (95% CI, 82.9%-88.4%) in the ABVD × 4 arm (HR, 0.523; 95% CI, 0.387-0.707; $P < .0001$; Figure 6). At a median follow-up of 104 months, the 10-year overall survival rates were still similar in the 2 arms: 94.0% in the 2+2 arm (95% CI, 92.3%-95.8%) vs 94.1% in the ABVD × 4 arm (95% CI, 92.3%-96.0%).

In the intention-to-treat analysis, the rates of first progression and relapse were 10.2% in the ABVD × 4 arm vs 3.4% in the 2+2 arm.

Deaths were reported in 4.8% of patients in the 2+2 group (n=53) and 5.4% of patients in the ABVD × 4 group (n=42). Study treatment was the cause of death in 0.6% of patients in the 2+2 group vs 0.1% of patients in the ABVD × 4 group. Deaths caused by toxicity from salvage therapy occurred in 0.6% vs 1.0%, respectively.

At a median observation time of 97 months, second primary malignancies had occurred in 6.4% of patients in the 2+2 arm and 4.7% of patients in the ABVD × 4 arm ($P = .8577$). The standard incidence ratios for second primary malignancy were 2.6 for the

ABSTRACT SUMMARY PET-Adapted Nivolumab or Nivolumab Plus ICE as First Salvage Therapy in Relapsed or Refractory Hodgkin Lymphoma

A trial evaluated PET-adapted nivolumab with or without ifosfamide, carboplatin, and etoposide (ICE) in patients with relapsed/refractory Hodgkin lymphoma (Abstract 239). The trial enrolled 43 adult patients, whose median age was 35 years. Enrolled patients had received only 1 line of systemic therapy. Their ECOG performance status was 2 or lower. Patients were treated with nivolumab alone (79%) or nivolumab plus ICE (21%) after frontline chemotherapy had failed. The CR rates were 78% for nivolumab and 88% for nivolumab plus ICE. The ORRs were 92% vs 100%, respectively. At the end of protocol therapy, the overall CR rate was 88% and the ORR was 90%. The CR rate was unexpectedly high, at 70%, when nivolumab was used as first salvage therapy, and most of these patients underwent ASCT without receiving ICE. At a median follow-up of 12 months, the PFS rate in the intention-to-treat population was 74% (95% CI, 55%-86%). No unexpected toxicities occurred. The most common AE potentially related to treatment with nivolumab plus ICE was grade 1 nausea, which was reported in approximately 75% of patients. Grade 1 vomiting occurred in approximately 62%. In 12% of patients, therapy was discontinued before the end of scheduled treatment.

2+2 arm and 2.3 for the ABVD × 4 arm, which are higher than the age- and sex-specific incidence ratios in the general German population. Deaths from a second malignancy occurred in 1.4% of patients (n=16) in the 2+2 arm and in 1.5% of patients (n=12) in the ABVD × 4 arm.

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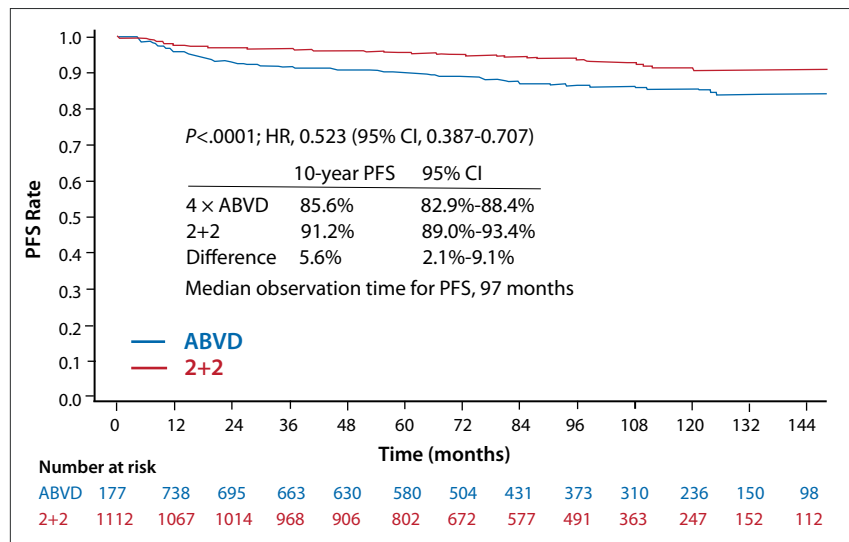


Figure 6. Long-term PFS in the GHSG HD14 trial, which compared 2 cycles of escalated BEACOPP followed by 2 cycles of ABVD (2+2) vs standard of care among patients with early unfavorable Hodgkin lymphoma. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; GHSg, German Hodgkin Study Group; HR, hazard ratio; PFS, progression-free survival. Adapted from Gillissen S et al. ASH abstract 129. *Blood*. 2019;134(suppl 1).¹

Brief Pembrolizumab Monotherapy Results in Complete and Near Complete Responses in the Majority of Untreated Patients With Classical Hodgkin Lymphoma: A Multicenter Phase 2 PET-Adapted Study of Sequential PEM and AVD

A multicenter phase 2 study evaluated induction therapy with a short course of pembrolizumab followed by AVD in patients with previously untreated classical Hodgkin lymphoma.¹ This regimen eliminates the need for bleomycin and radiotherapy consolidation. The investigator-initiated protocol (U16HO8) called for PET/CT-directed, frontline therapy with pembrolizumab followed by AVD chemotherapy. The primary endpoint was the complete metabolic response rate by PET/CT according to the Lugano criteria (with a Deauville score of 1-3 considered negative) after 3 doses of single-agent pembrolizumab. The secondary endpoints

included toxicity, PFS, overall survival, and response by metabolic tumor volume after pembrolizumab.

The trial enrolled adults with newly diagnosed, histologically confirmed classical Hodgkin lymphoma, including patients with early unfavorable disease according to criteria from the National Comprehensive Cancer Network or advanced-stage disease. Nearly half of patients (47%) had B symptoms at diagnosis. Exclusion criteria included prior chemotherapy, interstitial lung disease, prior autoimmune disease, organ dysfunction, and active infection. The target accrual of 30 patients was achieved. Therefore, the study had 84% power with

a 1-sided alpha of 10% to detect a doubling of the complete metabolic response rate from the 20% seen in the setting of relapse with single-agent pembrolizumab to the hypothesized 40% for this study.

Patients received a 200-mg dose of pembrolizumab every 3 weeks for 3 cycles, then underwent an interim PET/CT, which was centrally reviewed, for the primary analysis. The patients then received sequential therapy with AVD chemotherapy. Patients with advanced-stage disease received a total of 6 cycles. Those with early unfavorable disease received 4 cycles. Patients with early unfavorable and bulky disease had the option to

continue to 6 cycles. PET/CT was repeated after 2 cycles of AVD and at the end of therapy. Patients were evaluated every 3 months for 2 years.

The median age of the patients was 29 years (range, 21-77). Most patients were female (63%). Among the 30 patients, 12 had early unfavorable disease and 18 had advanced-stage disease. There were 5 patients with stage III disease and 13 patients with stage IV disease. Adverse risk factors for all patients included age older than 60 years (n=4), bulky disease (>10 cm; n=10) or a large mediastinal mass (>1/3; n=9), B symptoms at diagnosis (n=14), and extranodal involvement (n=16).

Following initial pembrolizumab monotherapy, the complete metabolic response rate was 37% (n=11, including 3 patients with large mediastinal masses),¹ which was 1 patient short of the primary endpoint. Additionally, 4 patients with bulky disease and 4 others had major reductions in disease, but they did not achieve a CR per the Lugano criteria. A partial metabolic response was observed in 18 patients.

An atypical response, with clearance of the original disease followed by the development of new sites of disease that cleared after AVD, was seen in 1 patient.

To better characterize the depth of response after treatment with pembrolizumab monotherapy, the investigators then quantified the decline in metabolic tumor volume. Among 28 patients, 20 had at least a 90% reduction in metabolic tumor volume (Figure 7). The investigators noted early deep responses, particularly in some patients with bulky disease. Significant heterogeneity was observed among the patients with a partial metabolic response; changes in metabolic tumor volume ranged from 50% to 98%.

After 2 cycles of AVD, the CR rate was 100%. The median duration of follow-up for patients who completed therapy was 8.2 months (range, 0.5-18.7). All CRs were maintained at the end of treatment. No deaths or cases of disease progression occurred. Therefore, the PFS and overall survival rates were both 100%.

All patients completed the proto-

col-directed therapy. Therapy was well tolerated, and most treatment-related AEs for pembrolizumab monotherapy were grade 1 or 2. Grade 2 AEs potentially related to treatment included infusion reactions (n=4); hypertension (n=4); anemia (n=2); hyperglycemia (n=2); nausea, vomiting, and/or diarrhea (n=2); thyroid disorders (n=2); neutropenia (n=1); and pericarditis (n=1; the patient had a history of this event). Grade 3 or 4 AEs potentially related to treatment included neutropenia (n=3); elevated liver function enzymes (n=1); Bell palsy (n=1); lymphopenia (n=1); and nausea, vomiting, and/or diarrhea (n=1). The study reported no serious AEs, no treatment discontinuations because of AEs, and no cases of pneumonitis or colitis.

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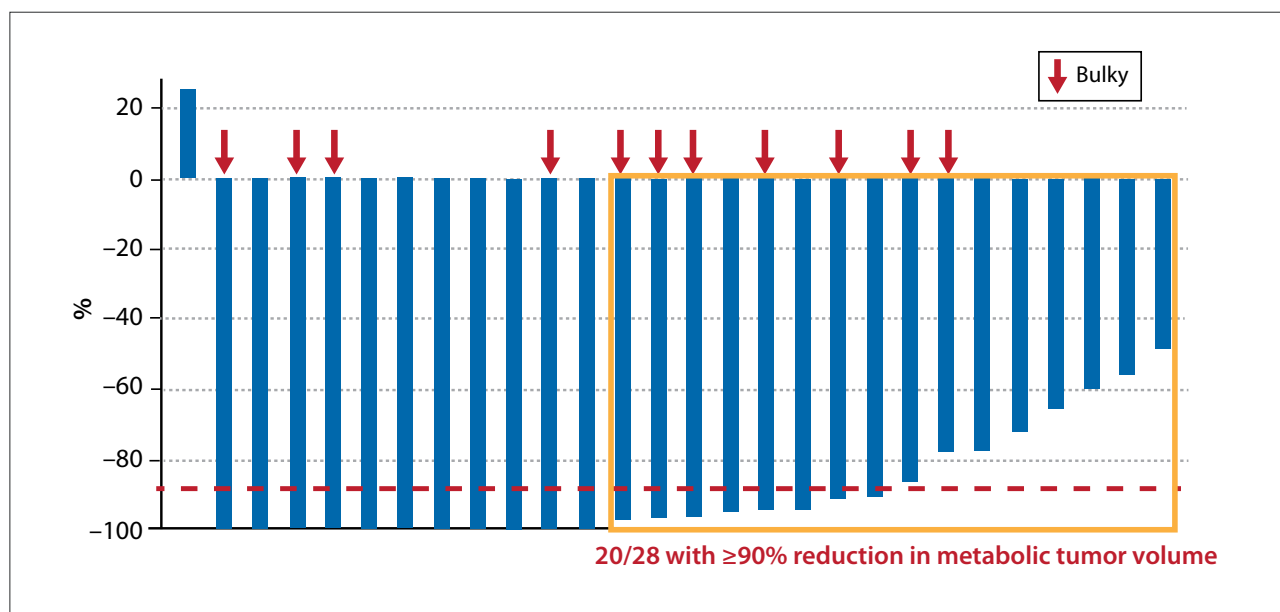


Figure 7. Change in metabolic tumor volume following induction with single-agent pembrolizumab in a phase 2 trial of patients with classical Hodgkin lymphoma. Adapted from Allen P et al. ASH abstract 235. *Blood*. 2019;134(suppl 1).¹

Nivolumab and AVD for Early-Stage Unfavorable Hodgkin Lymphoma (NIVAHL)

Investigators from the German Hodgkin Study Group presented results from the multicenter, phase 2 NIVAHL study (Nivolumab and AVD in Early-Stage Unfavorable Classical Hodgkin Lymphoma), which evaluated the efficacy of nivolumab combined with AVD and administered as either concomitant or sequential therapy among patients with early unfavorable classical Hodgkin lymphoma.^{1,2} In both treatment arms, the cycles of nivolumab plus AVD lasted 28 days, with administration on days 1 and 15 of each cycle. In the concomitant treatment arm (n=55), nivolumab plus AVD was given for 4 cycles. In the sequential treatment arm (n=54), nivolumab was given alone for a total of 4 times at 2-week intervals, followed by 2 cycles of nivolumab plus AVD, and then AVD for 2 cycles. In both treatment arms, 30 Gy of involved-site radiotherapy was given after completion of chemoimmunotherapy. Response was assessed at an interim analysis and after treatment in each arm.

The primary endpoint was the CR rate after the end of treatment on the basis of PET/CT analysis. The patients' median age was 27 years (range, 18-60), and 95% had stage IIA or stage IIB disease. The most common risk factors included 3 or more areas of nodal disease (69%) and an elevated erythrocyte sedimentation rate (48%). Bulky disease of 5 cm or more was reported in 67%.

At the end of treatment, among evaluable patients from the concomitant therapy arm (n=51), the CR rate was 90% (95% CI, 78.6%-96.7%; Figure 8). Among evaluable patients from the sequential therapy arm (n=50), the CR rate was 94% (95% CI, 83.5%-98.7%). The ORR was 100% with concomitant therapy and 98% with sequential therapy.

An early interim evaluation was conducted after 2 cycles of nivolumab plus AVD among patients treated with concomitant therapy and after completion of the nivolumab-only infusions in those who received sequential therapy. The CR rates were 87% with

concomitant therapy and 51% with sequential therapy.

The estimated rates of PFS at 12 months were 100% with concomitant therapy and 98% with sequential therapy. Rates of 12-month overall survival were 100% in each treatment arm.

Grade 3 to 4 organ toxicities were reported in 24% of patients in the concomitant therapy arm and 30% of those in the sequential therapy arm. The most common toxicities were hepatobiliary, gastrointestinal, skin, and nervous system events. Grade 4 leukopenia occurred in 56% of patients receiving concomitant therapy and in 41% of patients receiving sequential therapy. Serious AEs occurred in 38% vs 28%, respectively.

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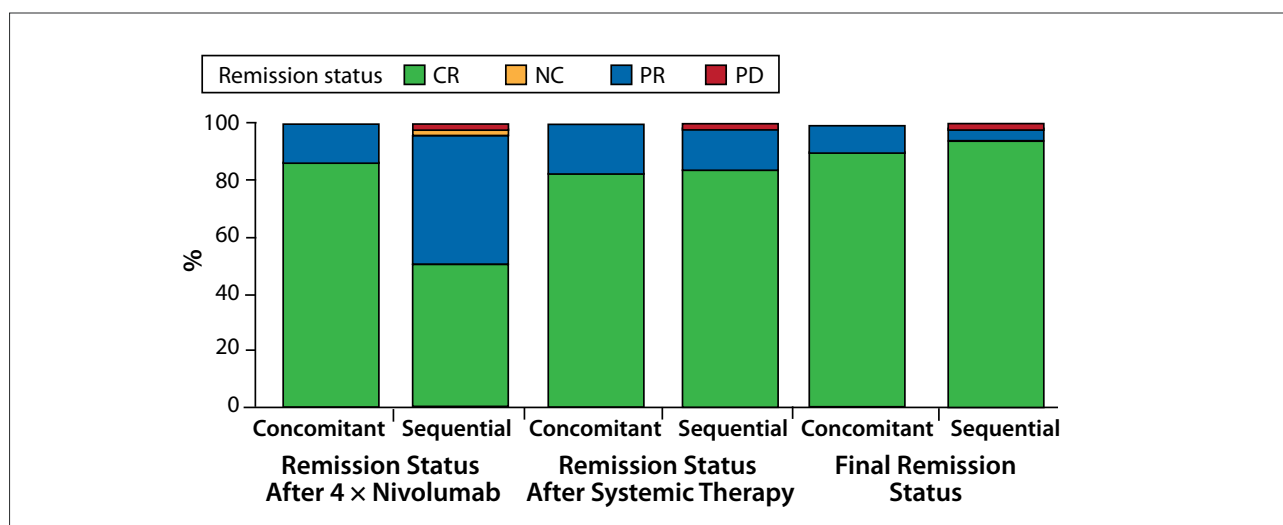


Figure 8. Response among patients with early-stage unfavorable Hodgkin lymphoma treated with nivolumab combined with AVD, administered as concomitant or sequential therapy. AVD, doxorubicin, vinblastine, and dacarbazine; CR, complete response; NC, no change; PD, progressive disease; PR, partial response. Adapted from Bröckelmann PJ et al. ASH abstract 236. *Blood*. 2019;134(suppl 1).¹

Reducing the Burden of Chemoradiotherapy With the Combination of Brentuximab Vedotin and Rituximab With Reduced-Toxicity Chemotherapy in Children, Adolescents, and Young Adults With Newly Diagnosed Hodgkin Lymphoma

Although the cure rates for patients with newly diagnosed classical Hodgkin lymphoma are high, the use of contemporary combined chemoradiotherapy regimens carries long-term toxicities that significantly impact quality of life and increase adverse health-related events, including death, following childhood therapy.¹ Previous data have shown the efficacy of brentuximab vedotin and rituximab in treatment-naïve adults with classical Hodgkin lymphoma.²⁻⁴ A phase 2 trial evaluated whether the addition of brentuximab vedotin and rituximab to risk-adapted chemotherapy would be well tolerated and effective in children, adolescents, and young adults with all stages of newly diagnosed classical Hodgkin lymphoma and would allow the elimination of more toxic chemotherapies (cyclophosphamide, etoposide, bleomycin) or radiation.⁵ The primary objectives of the study were evaluation of the safety and tolerability of the treatment combination and measurement of the overall CR and partial response rates.

The trial enrolled patients ages 1 to 30 years with all stages of newly diagnosed classical Hodgkin lymphoma.⁵ Patients were assigned to treatment regimens according to their risk: low (stages IA or IIA with no bulky disease or extension); intermediate (stages IA bulk/E, IB, IIA bulk/E, IIB, IIIA); or high (stages IIB bulk/E, IIIA bulk/E, IIIB, IVA/B). Patients classified as low risk received 3 cycles of brentuximab vedotin (1.2 mg/kg) with doxorubicin (25 mg/m²), vincristine (1.5 mg/m²), and dacarbazine (375 mg/m²) administered on days 1 and 15, plus prednisone (40 mg/m²/day) on days 1 through 14. Patients classified as intermediate or high risk received 4 or 6 cycles of

brentuximab vedotin (1.2 mg/kg), doxorubicin (25 mg/m²), vinblastine (6 mg/m²), and dacarbazine (375 mg/m²) administered on days 1 and 15, plus rituximab (375 mg/m²) on days 2 and 16. After completion of assigned chemoimmunotherapy cycles, patients with a CR did not receive radiation, unless they had high-risk, bulky disease and a slow response.

Patients were monitored for early response with PET/CT. Rapid early response was defined as a CR after completion of 1 cycle of chemotherapy for low-risk patients and after completion of 2 cycles of chemotherapy for intermediate- and high-risk patients.¹ CR was defined as resolution of pathological lymphadenopathy with at least an 80% reduction in the product of the perpendicular diameters of all of the nodal masses; absence of residual

disease in unmeasurable, assessable lesion sites; absence of new lesions; and PET negativity (Deauville score ≤ 3 , with ¹⁸F-fluorodeoxyglucose). Slow early response was defined as a partial response or stable disease after 1 cycle of chemotherapy for low-risk patients and 2 cycles of chemotherapy for intermediate- and high-risk patients.

At the time of the presentation, 33 patients were enrolled in the study. Most patients were female (n=21), and the median age was 15 years (range, 4-23). Risk was low in 4 patients, intermediate in 17, and high in 12. B symptoms were reported at diagnosis in 12 patients, and 11 patients had bulky disease.

The trial had enrolled 33 patients at the time of the report, and 32 had completed therapy. All 33 patients were evaluated for early response.⁵

ABSTRACT SUMMARY Brentuximab Vedotin in First Refractory/ Relapsed Classical Hodgkin Lymphoma Patients Treated by Chemotherapy (ICE) Before Autologous Transplantation: Final Analysis of a Phase II Study

A phase 2 trial evaluated brentuximab vedotin administered in combination with ICE chemotherapy as salvage treatment in relapsed or refractory classical Hodgkin lymphoma (Abstract 132). The trial enrolled 30 patients with relapsed disease and 12 with refractory disease. Patients received brentuximab vedotin plus ICE chemotherapy before undergoing ASCT. The primary endpoint was the complete metabolic response rate following 2 cycles of therapy according to the Lugano criteria. The patients' median age was 30 years. In an analysis of 39 patients, the complete metabolic response rate after 2 cycles was 69%. The rate of leukapheresis was 78.6%. The 1-year PFS rate was 69%, and the 1-year overall survival rate was 100%. The investigators did not identify any significant prognostic factors of response. Grade 3 or 4 AEs, reported in 83.3% of patients, consisted primarily of hematologic toxicities (71.4%) and infections (21.4%). Serious AEs occurred in 38.1% of patients. The most common serious AEs were infection (21.4%), hematologic toxicities (16.7%), and gastrointestinal disorders (7.1%). No deaths or neurologic toxicities occurred. Examination of metabolic tumor volume is ongoing.

The CR rate was 100%. A rapid early response was observed in 60% of patients, including 100% of those at low risk, 77% of those at intermediate risk, and 25% of those at high risk. Radiation therapy, administered based on the presence of bulky disease and a slow early response, was required in 4 patients, even though they had attained a CR before the start of radiation therapy. At a median follow-up of 48 months, the probability of event-free and overall survival was 100%.

Humoral and cellular immunity was also measured on completion of therapy. At a median follow-up of 18 months, the mean immunoglobulin G, CD19, and CD3 levels were all within normal range. Approximately 90% of patients in the study were able to avoid more toxic chemotherapy regimens and radiation.

Grade 3 mucositis occurred in 1 patient and grade 3 infusion reaction to brentuximab vedotin in 1 patient. Grade 3 peripheral neuropathy was observed in 2 patients. There were no reports of agammaglobulinemia, and no patient required hospitalization for systemic infection during or following treatment.

The study investigators concluded that the addition of brentuximab vedotin and rituximab to combination risk-adapted chemotherapy, without cyclophosphamide, etoposide, or bleomycin, appeared safe in children, adolescents, and young adults with newly

ABSTRACT SUMMARY Safety and Efficacy of Brentuximab Vedotin in Combination With AVD in Stage II-IV HIV-Associated Classical Hodgkin Lymphoma: Results of the Phase 2 Study, AMC 085

The phase 2 AMC-085 study evaluated brentuximab vedotin in combination with AVD in patients with stages 2 through 4 HIV-associated classical Hodgkin lymphoma (Abstract 130). Treatment was administered to 41 patients. The primary endpoint, the 2-year PFS rate, was 86%. The overall survival rate at 2 years was 92%. The CR rate was 100%. After cycle 2, 29 of 32 patients (90%) were PET/CT-negative. By the end of treatment, 28 of 29 patients (96%) were PET/CT-negative. Among patients with advanced-stage disease, the 2-year PFS rate was 87% and the 2-year overall survival rate was 90%. Safety appeared to be similar to that of the non-HIV population, with exceptions of increased rates of neutropenia and grade 1/2 peripheral neuropathy. Neutropenia occurred in 66% of patients and was grade 3 or higher in 57%. Peripheral sensory neuropathy was reported in 48% of patients and was grade 3 or higher in 10%. One fatality occurred during treatment. The study identified major interactions with strong CYP3A4/P-glycoprotein inhibitors. During treatment, there were increases in CD4-positive and CD8-positive T-cell counts. Viral load decreased from a median of 52 copies/mL at baseline to 40 copies/mL after treatment.

diagnosed classical Hodgkin lymphoma. For future studies, the investigators may omit radiation therapy for patients in CR after chemoimmunotherapy, redefine rapid early response to rely more on PET negativity than on size reduction criteria, and decrease the remaining doxorubicin doses for all patients.

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Combination of Oral Nanatinostat, a Novel Histone Deacetylase Inhibitor, and the Oral Anti-Viral, Valganciclovir, Is Active in Relapsed/Refractory Epstein-Barr Virus–Positive B-Cell, T-Cell, and Hodgkin Lymphoma: Interim Safety and Efficacy Results From a Phase 1b/2a Study

The combination of nanatinostat and valganciclovir showed tolerability and activity among patients with relapsed/refractory lymphoma associated with Epstein-Barr virus (EBV), according to recent phase 1b trial results.¹ Nanatinostat, an oral novel histone deacetylase inhibitor, can induce the expression of kinases encoded by EBV DNA that activate valganciclovir, converting valganciclovir into ganciclovir through phosphorylation.¹ Ganciclovir then halts DNA synthesis locally and kills affected cells.

The International Agency for Research on Cancer lists EBV as 1 of 6 infections identified as group 1 carcinogens.² EBV has been estimated to cause approximately 200,000 new cancer cases per year globally, and EBV was associated with 1.8% of cancer deaths worldwide in 2010.³⁻⁴ The presence of EBV nucleic acids has additionally been associated with poorer outcomes for patients in some reports across lymphoma types.⁵⁻⁷ However, the definition of EBV positivity has varied across studies, and has been associated with variable outcomes.¹

In this phase 1b portion of a phase 1b/2 open-label trial, 25 patients with relapsed/refractory EBV-positive lymphoma were divided into 5 cohorts, each receiving a different dose.¹ Disease subtypes included B-cell lymphoma in 12 patients, T-cell lymphoma in 8 patients, and Hodgkin lymphoma in 5 patients. Endpoints included safety, response rate, clinical benefit rate, and

response duration. The clinical benefit rate included CR, partial response, and stable disease rates. Responses were determined by evaluating PET/CT scans according to the Lugano criteria.

The median patient age in the phase 1b study was 58 years, and the median number of prior therapies was 2 (range, 1-9). A total of 3 patients had previously received a histone deacetylase inhibitor.

Efficacy in the phase 1b portion of the trial was evaluable in 18 patients. The ORR was 56%, with a CR rate of 28%. A CR was reported in patients with B-cell lymphoma, T-cell and natural killer–cell lymphoma, and Hodgkin lymphoma. Minor or stable disease was reported in 22%. The clinical benefit rate was 78%. Among the 15 patients who were HIV-negative, the ORR was 67%, and the CR rate was 33%. Minor or stable disease was reported in 22%. The clinical benefit rate was 93%. Among the patients who responded to treatment, the median duration of therapy was 6.5 months.

Safety was reported for the phase 1b cohort in combination with phase 2 data for 28 patients. Among 13 patients who had received nanatinostat at 10 mg/d and valganciclovir at 900 mg/d, grade 3 or 4 AEs included thrombocytopenia in 15%, neutropenia in 15%, and anemia in 8%. Among 7 patients who had received nanatinostat at 20 mg/d and valganci-

clovir at 1800 mg/d, grade 3 or 4 AEs included thrombocytopenia in 43%, neutropenia in 28%, anemia in 14%, and fatigue in 14%.

Among the 13 patients who received nanatinostat at 20 mg/d for the first 4 days of each cycle and valganciclovir at 900 mg daily, 1 patient (8%) had grade 3 or 4 neutropenia and 1 patient (8%) had grade 3 or 4 anemia. This dosing regimen was identified as the recommended phase 2 dose. Enrollment is currently ongoing for the phase 2 portion of the trial.

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Highlights in Hodgkin Lymphoma From the 61st American Society of Hematology Annual Meeting: Commentary

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Studies in Hodgkin lymphoma presented at the 61st American Society of Hematology (ASH) meeting provided new and updated data on treatments such as brentuximab vedotin, programmed death 1 (PD-1) inhibitors, and chemotherapy regimens. Some studies suggested that treatment with brentuximab vedotin and PD-1 inhibitors might reduce the need for chemotherapy in certain settings, and that the combination administered without chemotherapy is active in patients older than 59 years with newly diagnosed Hodgkin lymphoma.

Brentuximab Vedotin

A phase 2 study evaluated frontline brentuximab vedotin plus nivolumab in patients with Hodgkin lymphoma ages 60 years and older.¹ Approximately 20% of patients with Hodgkin lymphoma are older, and prognosis is somewhat worse in these patients. The trial enrolled 21 patients ages 60 to 88 years, with a median age of 72 years. Sixteen patients had stage 3 or 4 disease. The treatment consisted of standard doses of brentuximab vedotin and nivolumab given every 3 weeks for 4 doses. After initial treatment, patients underwent positron emission tomography/computed tomography (PET/CT). Patients continued with treatment after this assessment. The median number of cycles was 10, and

the range was 1 to 16. At the time of the report, 17 patients had discontinued treatment.

The median follow-up was 6.8 months. Among the 19 patients with a postbaseline assessment, the objective response rate was 95%. The complete response rate was 68%, which is better than that seen with single-agent brentuximab vedotin or nivolumab. These data exclude 3 patients with early progression, presumably before postbaseline response assessment.

There was 1 case of a treatment-related serious adverse event (pyrexia). Grade 3 or higher treatment-related adverse events included lipase elevations in 24%, peripheral motor neuropathy in 14%, peripheral sensory neuropathy in 14%, fatigue in 10%, and hyponatremia in 10%. The sensory and motor peripheral neuropathy were likely related to brentuximab vedotin. The lipase elevations, fatigue, and hyponatremia may be immune effects of nivolumab.

Dr Nancy L. Bartlett and colleagues presented 4-year results of the ECHELON-1 trial (A Frontline Therapy Trial in Participants With Advanced Classical Hodgkin Lymphoma), which compared brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (AVD) vs doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD).^{2,3} I was an investigator on this trial. Three-year results were presented at the 2018 American

Society of Clinical Oncology meeting and published in *Blood*.^{4,5} The 4-year results are similar to the 3-year results. This large, international randomized trial enrolled more than 1300 patients. The primary endpoint, 2-year modified progression-free survival (PFS), was presented at the ASH meeting 3 years ago.⁶ Treatment with brentuximab vedotin plus AVD resulted in a statistically significant 5% improvement in modified PFS at 2 years. These data led the US Food and Drug Administration to approve brentuximab vedotin plus AVD as frontline treatment for stage 3/4 Hodgkin lymphoma.

This difference was maintained in further follow-up. At both 3 and 4 years, the improvement with brentuximab vedotin plus AVD was approximately 7%, and the *P* value increased. At the longer follow-up durations of 3 and 4 years, brentuximab vedotin plus AVD was superior to ABVD in all subgroups, including patients with adverse risk factors, such as a high International Prognostic Score, stage 3/4 disease, and male sex.

The patients underwent PET at screening, at the end of cycle 2, and at the end of treatment. An interesting finding from this study is that the interim PET scan did not necessarily lead to a change in treatment. At the time of the interim PET analysis, 89% of patients in the brentuximab vedotin arm and 86% of those in the ABVD arm were PET-negative. For PET-neg-

ative patients, the PFS at 4 years was 84.5% with brentuximab vedotin plus AVD vs 78.9% with ABVD ($P=.006$). Among the PET-positive patients, PFS was 59.8% for those treated with brentuximab vedotin plus AVD vs 44.5% for those treated with ABVD ($P=.164$). This trial was not risk-adapted with a change in treatment for patients who were interim PET-positive. The difference in PFS for PET-positive patients between the brentuximab vedotin plus AVD group and the ABVD group was not statistically significant. There is currently no treatment that can increase PFS from 60% to 70% for PET-positive patients and from 85% for PET-negative patients. The study investigators concluded that it is possible to dispense with interim PET, and to treat all patients with 6 cycles of brentuximab vedotin plus AVD. This strategy can avoid the complexities of performing an interim PET scan, particularly the difficulties in interpreting a positive scan among patients receiving ABVD.

My colleague Dr Alison J. Moskowitz presented follow-up results for a phase 1/2 trial of brentuximab vedotin in combination with nivolumab in patients with relapsed/refractory Hodgkin lymphoma.⁷ Earlier results were published by Dr Alex F. Herrera.⁸ The trial enrolled 93 patients with relapsed or refractory Hodgkin lymphoma after 1 line of therapy. Patients underwent PET after 2 cycles and 4 cycles. The overall response rate was 85%, with a complete response rate of 67%. This complete response rate is higher than that seen with single-agent brentuximab vedotin or nivolumab. Among the patients with a complete response, 67% went on to receive autologous transplant without other chemotherapy. The 17 patients without a complete response received further salvage chemotherapy and then underwent autologous transplant. After transplant, 10 patients received consolidation therapy with brentuximab vedotin, a strategy used in the

AETHERA trial (A Phase 3 Study of Brentuximab Vedotin [SGN-35] in Patients at High Risk of Residual Hodgkin Lymphoma Following Stem Cell Transplant),⁹ 4 patients received nivolumab maintenance, and 2 patients received radiation therapy.

For all patients, the 2-year PFS was 79% and the 2-year overall survival was 94%. The 2-year PFS for the patients treated with brentuximab vedotin and nivolumab followed by autologous transplant without further chemotherapy was 92%.

Grade 1 peripheral sensory neuropathy occurred in 18% of patients. Neutropenia was reported in 7% of patients, and 5 cases were grade 3 or 4. Grade 3 episodes of peripheral neuropathy and elevated gamma-glutamyl transpeptidase each required 1 patient to discontinue treatment. Serious adverse events were reported in 15%. Pneumonia, pneumonitis, and pyrexia each occurred in 2 patients. There was one report of Guillain-Barré syndrome following treatment, a side effect of nivolumab. This case was improving at the time of the report. Corticosteroids for autoimmune events were required by 14% of patients. As shown by other studies, checkpoint inhibitors are associated with autoimmune events.

Dr Paul G. Rubinstein and colleagues presented results of a phase 2 study evaluating the efficacy and safety of brentuximab vedotin plus AVD in patients with stages II through IV HIV-associated classical Hodgkin lymphoma.¹⁰ Previous data have shown that standard treatments for patients with HIV and Hodgkin lymphoma in the era of highly active antiretroviral therapy (HAART) are similar to those for non-HIV positive patients,¹¹ which represents a major change from the time before HAART was available. Patients with HIV have an increased risk of Hodgkin lymphoma, and the disease is usually at an advanced stage. This trial evaluated brentuximab vedotin plus AVD. In the ECHELON-1 trial of non-HIV patients, this regi-

men was superior to ABVD by a small amount that was statistically significant.² All patients in the trial reported by Dr Rubinstein received prophylaxis with granulocyte-colony stimulating factor. Among the 41 patients enrolled, 83% were stages 3/4. At the time of enrollment, 69% of patients had undetectable viral loads. Patients had somewhat more peripheral neuropathy vs the non-HIV positive population in the ECHELON-1 trial.

At 2 years, PFS was 86% and overall survival was 92%. These data suggest that this newer regimen is a safe and effective option for the HIV population. The rate of serious adverse events was 54% in this trial vs 33% in the ECHELON-1 trial.^{2,10} Many of these events consisted of hospitalizations, mostly for fever. The study identified strong interactions between brentuximab vedotin plus AVD and drugs that impact CYP3A4, which is the drug metabolizing system in the liver, and P-glycoprotein inhibitors.

The Lymphoma Study Association (LYSA) French cooperative group presented data from a phase 1/2 feasibility study evaluating the addition of brentuximab vedotin to ifosfamide, carboplatin, and etoposide (ICE) in patients with relapsed/refractory Hodgkin lymphoma.¹² Patients had primary refractory disease after first-line chemotherapy or were in first relapse after a polychemotherapy regimen. Patients received 2 cycles of brentuximab vedotin plus ICE. ICE is a standard pretransplant regimen developed at Memorial Sloan Kettering Cancer Center.¹³ Patients without a complete metabolic response, according to PET, exited the study. Patients with a complete metabolic response received 3 more cycles of brentuximab vedotin and ICE, followed by additional treatment with brentuximab vedotin. Patients then underwent transplant.

Patients received a total of 5 cycles of ICE. In comparison, we typically administer 2 cycles of ICE to patients

with Hodgkin lymphoma. This regimen tends to be cumulatively toxic. The phase 1 portion of the study compared 2 doses of brentuximab vedotin: 1.2 mg/kg and 1.8 mg/kg. The higher dose was selected for the phase 2 study. Among the 42 patients in the study, 69% achieved a complete metabolic response. At 1 year, the PFS was 69% and the overall survival was 100%, with a short follow-up. In comparison, the standard transplant strategy results in a PFS of approximately 50%.

Grade 3/4 adverse events were reported in 83% of patients, which is a high amount. Serious adverse events occurred in 38%. There were no deaths or cases of neurologic toxicity. The dose of brentuximab vedotin was relatively low, so it is not surprising that neurologic toxicity did not occur. This regimen had a high amount of toxicity, which is not surprising given that 5 cycles of ICE were administered. It is difficult to say whether this strategy represents an improvement over more traditional approaches.

Chemotherapy Regimens

The German Hodgkin Study Group presented a long-term follow-up analysis of the HD14 trial of patients with early-stage, unfavorable Hodgkin lymphoma.¹⁴ This trial compared 4 cycles of ABVD plus radiation therapy, a standard treatment established in a previous trial,¹⁵ with 2 cycles of more intensive treatment with escalated BEACOPP followed by 2 cycles of ABVD and radiation therapy. The 5-year rate of PFS was 89.3% for the standard treatment vs 95.3% for the more intensive treatment. This difference is small. There was no significant difference in overall survival. It should be noted that no randomized clinical trials in Hodgkin lymphoma studies have demonstrated a survival difference as an endpoint of the trial because outcomes are always excellent.

The long-term follow-up identified no differences in deaths, toxicities,

treatment-related mortality, second malignancies, or female infertility, which is a known concern with escalated BEACOPP. The trial provided data for 1889 patients. The median follow-up was long, at 104 months. The estimated 10-year PFS was 85.6% with standard ABVD and radiation therapy vs 91.2% with BEACOPP, ABVD, and radiation therapy. This difference was small, but still statistically significant based on the large number of patients in the study. The overall survival for both groups was 94%.

Although the difference in PFS was statistically significant, the improvement may not be clinically important. To me, these data suggest that the more aggressive treatment was not beneficial. At my institution, we have treated patients with chemotherapy alone, without radiation therapy, using interim and end-of-treatment PET to document response.

PD-1 Inhibitors

A multi-institutional study evaluated pembrolizumab monotherapy administered prior to doxorubicin, vinblastine, and dacarbazine (AVD), without bleomycin.¹⁶ This small trial enrolled 30 patients with Hodgkin lymphoma with early-stage, unfavorable, and advanced-stage disease who had not received prior treatment. Patients received 3 doses of pembrolizumab, followed by 2 cycles of AVD. Patients with early-stage unfavorable disease received 2 more cycles of AVD. Patients with advanced-stage disease received a total of 6 doses of AVD. Elderly patients with less than a complete metabolic response or who received less than 4 cycles of AVD were treated with pembrolizumab for 1 to 2 years as maintenance therapy.

The median follow-up was 8.2 months. All patients were PET-negative after 2 cycles of AVD and at the end of treatment. Pembrolizumab monotherapy led to complete meta-

bolic response in 37% of patients. An additional 30% of patients had more than 90% regression. The response rate was 100% for patients with early-stage disease who received at least 4 cycles of AVD. Among patients with advanced-stage disease, who received 6 cycles of AVD, the complete metabolic response rate was 75%. This trial demonstrates that pembrolizumab monotherapy can induce complete responses in previously untreated Hodgkin lymphoma.

The German Hodgkin Study Group presented results from a phase 1/2 trial of nivolumab and AVD plus radiation therapy in early-stage, unfavorable Hodgkin lymphoma.¹⁷ One treatment arm consisted of nivolumab and AVD administered concurrently for 4 cycles, followed by involved-site radiation therapy (30 Gy). The other arm consisted of sequential treatment: 2 cycles of nivolumab monotherapy, 2 cycles of nivolumab plus AVD, and then 2 cycles of AVD alone.

Both treatment schedules were associated with toxicity that may have been autoimmune-related. Grade 1 to 2 organ toxicity was reported in 60% of the concomitant arm and 63% of the sequential arm. These toxicities included hepatobiliary, pancreatic, gastrointestinal tract, skin, and nervous system events. Grade 1 to 2 respiratory tract toxicity, which may have been immune-related pneumonitis, occurred in 22% of patients in both groups. Grade 3 adverse events occurred in 20% of the concomitant group and 28% of the sequential group. Serious adverse events (almost all requiring hospitalization) occurred in 38% vs 28%, respectively. The checkpoint inhibitors have autoimmune effects that can sometimes be fatal. No deaths were reported.

The overall response rate was 100% for concomitant treatment and 98% for sequential treatment. The 12-month estimated PFS was 100% vs 98%, respectively. A complete response was seen in 87% of patients in the concomitant arm and 51% of patients

in the sequential group after 4 doses of nivolumab. There can be pseudoprogression or nonresponse with checkpoint inhibitors, and it is noteworthy that 5 patients in the concomitant arm who were not complete metabolic responders but were in partial remission had ongoing remissions at the time of the report. PET scans may not be a good way of assessing response to treatment with PD-1 inhibitors.

Dr Alex F. Herrera and colleagues presented a study evaluating nivolumab administered alone or with ICE before transplant after frontline treatment.¹⁸ Patients received 2 doses of nivolumab and then underwent PET/CT. Patients with a complete or partial response received an additional 2 cycles of nivolumab. Those with a complete response then underwent autologous transplant. Patients with less than a complete response received a combination of nivolumab plus ICE for 3 cycles. They then underwent another PET scan. Patients with a complete response underwent transplant. Those who did not exit the study. Among the 43 patients, 79% proceeded to transplant after treatment with nivolumab only. Among the patients who received additional treatment with nivolumab plus ICE, 9 more underwent transplant. Overall, 70% of patients underwent transplant. The overall response rate was 100%, with a complete metabolic response in 88%. In the combination arm, at the end of treatment, all 8 patients had an objective response, and 7 of 8 patients

had a complete response. At a median follow-up of 12 months, the 1-year PFS was 74%.

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