

A SPECIAL MEETING REVIEW EDITION

Highlights in Lymphoma From the 60th American Society of Hematology Annual Meeting

A Review of Selected Presentations From the 60th American Society of Hematology Annual Meeting • December 1-4, 2018 • San Diego, California

Special Reporting on:

- The ECHELON-2 Trial: Results of a Randomized, Double-Blind, Active-Controlled Phase 3 Study of Brentuximab Vedotin and CHP (A+CHP) Versus CHOP in the Frontline Treatment of Patients With CD30+ Peripheral T-Cell Lymphomas
- Rituximab/Bendamustine and Rituximab/Cytarabine Induction Chemotherapy for Transplant-Eligible Patients With Mantle Cell Lymphoma: A Pooled Analysis of Two Phase 2 Clinical Trials and Off-Trial Experience
- Nivolumab Combined With Brentuximab Vedotin for Relapsed/Refractory Primary Mediastinal Large B-Cell Lymphoma: Preliminary Results From the Phase 2 CheckMate 436 Trial
- Axicabtagene Ciloleucef CD19 Chimeric Antigen Receptor (CAR) T-Cell Therapy for Relapsed/Refractory Large B-Cell Lymphoma: Real World Experience
- Venetoclax Plus Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone (R-CHOP) Improves Outcomes in BCL2-Positive First-Line Diffuse Large B-Cell Lymphoma: First Safety, Efficacy, and Biomarker Analyses From the Phase II CAVALLI Study
- Response-Adapted Therapy With Nivolumab and Brentuximab Vedotin (BV), Followed By BV and Bendamustine for Suboptimal Response, in Children, Adolescents, and Young Adults With Standard-Risk Relapsed/Refractory Classical Hodgkin Lymphoma
- A Phase I Study With an Expansion Cohort of the Combinations of Ipilimumab, Nivolumab, and Brentuximab Vedotin in Patients With Relapsed/Refractory Hodgkin Lymphoma: A Trial of the ECOG-ACRIN Research Group (E4412: Arms G-I)
- Brentuximab Vedotin Plus Chemotherapy in Patients With Advanced-Stage Classical Hodgkin Lymphoma: Evaluation of Modified Progression-Free Survival and Traditional PFS in the Phase 3 ECHELON-1 Study

PLUS Meeting Abstract Summaries

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ON THE WEB:
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Brentuximab vedotin (ADCETRIS®) + CHP recommended by NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for frontline PTCL
Category 1 for ALCL and Category 2A for CD30+ histologies other than ALCL¹

In frontline sALCL and other CD30-expressing peripheral T-cell lymphomas (PTCL)

REACH FOR EXTENDED SURVIVAL

ADCETRIS + CHP vs CHOP:



29%

reduction in risk of PFS event*

(HR: 0.71; 95% CI: 0.54, 0.93; $P = 0.011$); median PFS 48.2 vs 20.8 months for A+CHP and CHOP, respectively; primary endpoint²

*PFS was defined as time from randomization to progression, death due to any cause, or receipt of subsequent anticancer therapy to treat residual or progressive disease.²

Indication

ADCETRIS® (brentuximab vedotin) is indicated for the treatment of adult patients with previously untreated systemic anaplastic large cell lymphoma or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone.

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.

Explore clinical data at

adcetrispro.com



34%

reduction in risk of death

(HR = 0.66; 95% CI: 0.46, 0.95; $P = 0.024$); key secondary endpoint^{†2}

[†]Median overall survival follow-up of 42.1 months with A+CHP and CHOP; median overall survival not reached in either treatment arm.³

ECHELON-2 trial design: A multicenter, phase 3, randomized, double-blind, double-dummy, actively controlled trial in 452 patients with sALCL and other CD30-expressing PTCL. Patients were randomized 1:1 to A+CHP (n = 226) or CHOP (n = 226), and received treatment every 3 weeks for 6 to 8 cycles at investigator's discretion. Primary endpoint was PFS per IRF, defined as progression, death from any cause, or receipt of subsequent anticancer therapy to treat residual or progressive disease. Overall survival was a key secondary endpoint.^{2,3}

Most common adverse reactions (≥20%) in combination with CHP

Anemia, neutropenia, peripheral neuropathy, lymphopenia, nausea, diarrhea, fatigue or asthenia, mucositis, constipation, alopecia, pyrexia, and vomiting.²

A+CHP = ADCETRIS + cyclophosphamide, doxorubicin, prednisone; ALCL = anaplastic large cell lymphoma; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CHP = cyclophosphamide, doxorubicin, prednisone; CI = confidence interval; HR = hazard ratio; IRF = independent review facility; PFS = progression-free survival; sALCL = systemic anaplastic large cell lymphoma.

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

CD30-DIRECTED
ADCETRIS[®]
brentuximab vedotin 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 classical Hodgkin Lymphoma or previously untreated PTCL.

Monitor complete blood counts prior to each ADCETRIS dose. Monitor more frequently for patients with Grade 3 or 4 neutropenia. Monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent doses.

- **Serious infections and opportunistic infections:** Infections such as pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes) have been reported in ADCETRIS-treated patients. Closely monitor patients during treatment for bacterial, fungal, or viral infections.
- **Tumor lysis syndrome:** Closely monitor patients with rapidly proliferating tumor and high tumor burden.
- **Increased toxicity in the presence of severe renal impairment:** The frequency of \geq Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. Avoid use in patients with severe renal impairment.
- **Increased toxicity in the presence of moderate or severe hepatic impairment:** The frequency of \geq Grade 3 adverse reactions and deaths was greater in patients with moderate or severe hepatic impairment compared to patients with normal hepatic function. Avoid use in patients with moderate or severe hepatic impairment.
- **Hepatotoxicity:** Fatal and serious cases have occurred in ADCETRIS-treated patients. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, and occurred after the first ADCETRIS dose or rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may increase the risk. Monitor liver enzymes and bilirubin. Patients with new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCETRIS.
- **PML:** Fatal cases of JC virus infection resulting in PML have been reported in ADCETRIS-treated patients. First onset of symptoms occurred at various times from initiation of ADCETRIS, with some cases occurring within 3 months of initial exposure. In addition to ADCETRIS therapy, other possible contributory factors include prior therapies and underlying disease that may cause immunosuppression. Consider PML diagnosis in patients with new-onset signs and symptoms of central nervous system abnormalities. Hold ADCETRIS if PML is suspected and discontinue ADCETRIS if PML is confirmed.
- **Pulmonary toxicity:** Fatal and serious events of noninfectious pulmonary toxicity, including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome, have been reported. Monitor patients for signs and symptoms, including cough and dyspnea. In the event of new or worsening pulmonary symptoms, hold ADCETRIS dosing during evaluation and until symptomatic improvement.

- **Serious dermatologic reactions:** Fatal and serious cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with ADCETRIS. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.
- **Gastrointestinal (GI) complications:** Fatal and serious cases of acute pancreatitis have been reported. Other fatal and serious GI complications include perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, neutropenic colitis, and ileus. Lymphoma with preexisting GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, including severe abdominal pain, perform a prompt diagnostic evaluation and treat appropriately.
- **Embryo-fetal toxicity:** Based on the mechanism of action and animal studies, ADCETRIS can cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus, and to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Most Common ($\geq 20\%$ 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 the following pages and full Prescribing Information at adcetrispro.com

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for T-Cell Lymphomas (V.2.2019). © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed December 19, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. 2. ADCETRIS [Prescribing Information]. Bothell, WA: Seattle Genetics, Inc. November 2018. 3. Horwitz S, O'Connor OA, Pro B, et al; for the ECHELON-2 Study Group. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. December 3, 2018. *Lancet*. doi: 10.1016/S0140-6736(18)32984-2.

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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 systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone.

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 1.8 mg/kg up to a maximum of 180 mg in combination with cyclophosphamide, doxorubicin, and prednisone (CHP), administered every 3 weeks with each cycle of chemotherapy for 6 to 8 doses.

Reduce the dose in patients with mild hepatic impairment (Child-Pugh A) to 1.2 mg/kg up to a maximum of 120 mg every 3 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 PTCL who are treated with ADCETRIS + CHP, administer G-CSF beginning with Cycle 1.

2.3 Dose Modification

Peripheral Neuropathy: For Grade 2 motor neuropathy, reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks. For Grade 3 sensory neuropathy, reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks. For Grade 3 motor neuropathy, discontinue dosing. For Grade 4 sensory or motor 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-2 (Study 6), 52% of patients treated with ADCETRIS + CHP experienced new or worsening peripheral neuropathy of any grade (by maximum grade, 34% Grade 1, 15% Grade 2, 3% Grade 3, <1% Grade 4). The peripheral neuropathy was predominantly sensory (94% sensory, 16% motor) and had a median onset time of 2 months (range, <1-5). At last evaluation, 50% had complete resolution of neuropathy, 12% had partial improvement, and 38% had no improvement. The median time to resolution or improvement overall was 4 months (range, 0-45). Of patients with residual neuropathy at their last evaluation, the neuropathy was Grade 1 in 72%, Grade 2 in 25%, and Grade 3 in 3%.

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 classical Hodgkin lymphoma (cHL) or previously untreated PTCL.

Monitor complete blood counts prior to each dose of ADCETRIS. Monitor more frequently for patients with Grade 3 or 4 neutropenia. Monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent ADCETRIS doses.

5.4 Serious Infections and Opportunistic Infections

Serious infections and opportunistic infections such as pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes) have been reported in patients treated with ADCETRIS. Monitor patients closely during treatment for the emergence of possible bacterial, fungal, or viral infections.

5.5 Tumor Lysis Syndrome

Patients with rapidly proliferating tumor and high tumor burden may be at increased risk of tumor lysis syndrome. Monitor closely and take appropriate measures.

5.6 Increased Toxicity in the Presence of Severe Renal Impairment

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

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

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

5.8 Hepatotoxicity

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

5.9 Progressive Multifocal Leukoencephalopathy

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

5.10 Pulmonary Toxicity

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

5.11 Serious Dermatologic Reactions

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

5.12 Gastrointestinal Complications

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

5.13 Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, ADCETRIS can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of ADCETRIS in pregnant women. 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 ($\geq 20\%$) in combination with CHP were anemia, neutropenia, peripheral neuropathy, lymphopenia, nausea, diarrhea, fatigue or asthenia, mucositis, constipation, alopecia, pyrexia, and vomiting.

Previously Untreated sALCL or Other CD30-Expressing PTCL (Study 6, ECHELON-2)

ADCETRIS in combination with CHP was evaluated in patients with previously untreated, CD30-expressing PTCL in a multicenter, randomized, double-blind, double-dummy, actively controlled trial. Patients were randomized to receive ADCETRIS + CHP or CHOP for 6 to 8, 21-day cycles. ADCETRIS was administered on Day 1 of each cycle, with a starting dose of 1.8 mg/kg intravenously over 30 minutes, approximately 1 hour after completion of CHP. The trial required hepatic transaminases ≤ 3 times upper limit of normal (ULN), total bilirubin ≤ 1.5 times ULN, and serum creatinine ≤ 2 times ULN and excluded patients with Grade 2 or higher peripheral neuropathy.

A total of 449 patients were treated (223 with ADCETRIS + CHP, 226 with CHOP), with 6 cycles planned in 81%. In the ADCETRIS + CHP arm, 70% of patients received 6 cycles, and 18% received 8 cycles. Primary prophylaxis with G-CSF was administered to 34% of ADCETRIS + CHP-treated patients and 27% of CHOP-treated patients.

Fatal adverse reactions occurred in 3% of patients in the A+CHP arm and in 4% of patients in the CHOP arms, most often from infection. Serious adverse reactions were reported in 38% of ADCETRIS + CHP-treated patients and 35% of CHOP-treated patients. Serious adverse reactions occurring in $>2\%$ of ADCETRIS + CHP-treated patients included febrile neutropenia (14%), pneumonia (5%), pyrexia (4%), and sepsis (3%).

The most common adverse reactions observed $\geq 2\%$ more in recipients of ADCETRIS + CHP were nausea, diarrhea, fatigue or asthenia, mucositis, pyrexia, vomiting, and anemia. Other common ($\geq 10\%$) adverse reactions observed $\geq 2\%$ more with ADCETRIS + CHP were febrile neutropenia, abdominal pain, decreased appetite, dyspnea, edema, cough, dizziness, hypokalemia, decreased weight, and myalgia.

In recipients of ADCETRIS + CHP, adverse reactions led to dose delays of ADCETRIS in 25% of patients, dose reduction in 9% (most often for peripheral neuropathy), and discontinuation of ADCETRIS with or without the other components in 7% (most often from peripheral neuropathy and infection).

Table 7: Adverse Reactions Reported in $\geq 10\%$ of ADCETRIS + CHP-treated Patients with Previously Untreated, CD30-expressing PTCL (Study 6, ECHELON-2)

| Adverse Reaction | ADCETRIS + CHP Total N = 223 % of patients | | | CHOP Total N = 226 % of patients | | |
|-------------------------------------------------------------|--------------------------------------------------|---------|---------|----------------------------------------|---------|---------|
| | Any Grade | Grade 3 | Grade 4 | Any Grade | Grade 3 | Grade 4 |
| Blood and lymphatic system disorders | | | | | | |
| Anemia ^a | 66 | 13 | <1 | 59 | 12 | <1 |
| Neutropenia ^a | 59 | 17 | 22 | 58 | 14 | 22 |
| Lymphopenia ^a | 51 | 18 | 1 | 57 | 19 | 2 |
| Febrile neutropenia | 19 | 17 | 2 | 16 | 12 | 4 |
| Thrombocytopenia ^a | 17 | 3 | 3 | 13 | 3 | 2 |
| Gastrointestinal disorders | | | | | | |
| Nausea | 46 | 2 | - | 39 | 2 | - |
| Diarrhea | 38 | 6 | - | 20 | <1 | - |
| Mucositis | 30 | 2 | <1 | 27 | 3 | - |
| Constipation | 29 | <1 | <1 | 30 | 1 | - |
| Vomiting | 26 | <1 | - | 17 | 2 | - |
| Abdominal pain | 17 | 1 | - | 13 | <1 | - |
| Nervous system disorders | | | | | | |
| Peripheral neuropathy | 52 | 3 | <1 | 55 | 4 | - |
| Headache | 15 | <1 | - | 15 | <1 | - |
| Dizziness | 13 | - | - | 9 | <1 | - |
| General disorders and administration site conditions | | | | | | |
| Fatigue or asthenia | 35 | 2 | - | 29 | 2 | - |
| Pyrexia | 26 | 1 | <1 | 19 | - | - |
| Edema | 15 | <1 | - | 12 | <1 | - |
| Infections and infestations | | | | | | |
| Upper respiratory tract infection | 14 | <1 | - | 15 | <1 | - |

Table 7: Adverse Reactions, cont'd

| Adverse Reaction | ADCETRIS + CHP Total N = 223 % of patients | | | CHOP Total N = 226 % of patients | | |
|--------------------------------------------------------|--------------------------------------------------|---------|---------|----------------------------------------|---------|---------|
| | Any Grade | Grade 3 | Grade 4 | Any Grade | Grade 3 | Grade 4 |
| Skin and subcutaneous disorders | | | | | | |
| Alopecia | 26 | - | - | 25 | 1 | - |
| Rash | 16 | 1 | <1 | 14 | 1 | - |
| Musculoskeletal and connective tissue disorders | | | | | | |
| Myalgia | 11 | - | - | 8 | - | - |
| Respiratory, thoracic and mediastinal disorders | | | | | | |
| Dyspnea | 15 | 2 | - | 11 | 2 | - |
| Cough | 13 | <1 | - | 10 | - | - |
| Metabolism and nutrition disorders | | | | | | |
| Decreased appetite | 17 | 1 | - | 12 | 1 | - |
| Hypokalemia | 12 | 4 | - | 8 | <1 | <1 |
| Investigations | | | | | | |
| Weight decreased | 12 | <1 | - | 8 | <1 | - |
| Psychiatric disorders | | | | | | |
| Insomnia | 11 | - | - | 14 | - | - |

^aDerived from laboratory values and adverse reaction data. Laboratory values were obtained at the start of each cycle and end of treatment.

The table includes a combination of grouped and ungrouped terms. CHP = cyclophosphamide, doxorubicin, and prednisone; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone. Events were graded using the NCI CTCAE Version 4.03.

Additional Important Adverse Reactions

Infusion Reactions

In a study of ADCETRIS in combination with CHP (Study 6, ECHELON-2), infusion-related reactions were reported in 10 patients (4%) in the ADCETRIS + CHP-treated arm: 2 (1%) patients with events that were Grade 3 or higher events, and 8 (4%) patients with events that were less than Grade 3.

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 (doxorubicin, bleomycin, vinblastine, dacarbazine). Patients typically reported cough and dyspnea. Interstitial infiltration and/or inflammation were observed on radiographs and computed tomographic imaging of the chest. Most patients responded to corticosteroids. The concomitant use of ADCETRIS with bleomycin is contraindicated.

In a study of ADCETRIS in combination with CHP (Study 6, ECHELON-2), non-infectious pulmonary toxicity events were reported in 5 patients (2%) in the ADCETRIS + CHP arm; all 5 events were pneumonitis.

6.2 Post Marketing Experience

The following adverse reactions have been identified during post-approval use of ADCETRIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: febrile neutropenia.

Gastrointestinal disorders: acute pancreatitis and gastrointestinal complications (including fatal outcomes).

Hepatobiliary disorders: hepatotoxicity.

Infections: PML, serious infections and opportunistic infections.

Metabolism and nutrition disorders: hyperglycemia.

Respiratory, thoracic and mediastinal disorders: noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and ARDS (some with fatal outcomes).

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

6.3 Immunogenicity

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

Patients with cHL and sALCL in Studies 1 and 2 were tested for antibodies to brentuximab vedotin every 3 weeks using a sensitive electrochemiluminescence immunoassay. Approximately 7% of patients in these trials developed persistently positive antibodies (positive test at more than 2 time points) and 30% developed transiently positive antibodies (positive at 1 or 2 post-baseline time points). The anti-brentuximab antibodies were directed against the antibody component of brentuximab vedotin in all patients with transiently or persistently positive antibodies. Two of the patients (1%) with persistently positive antibodies experienced adverse reactions consistent with infusion reactions that led to discontinuation of treatment. Overall, a higher incidence of infusion-related reactions was observed in patients who developed persistently positive antibodies.

A total of 58 patient samples that were either transiently or persistently positive for anti-brentuximab vedotin antibodies were tested for the presence of neutralizing antibodies. Sixty-two percent (62%) of these patients had at least one sample that was positive for the presence of neutralizing antibodies. The effect of anti-brentuximab vedotin antibodies on safety and efficacy is not known.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on ADCETRIS

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

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 CHP for patients with previously untreated, CD30-expressing PTCL (Study 6: ECHOLON-2), 31% of ADCETRIS + CHP-treated patients were age 65 or older. Among older patients, 74% had adverse reactions \geq Grade 3 and 49% had serious adverse reactions. Among patients younger than age 65, 62% had adverse reactions \geq Grade 3 and 33% had serious adverse reactions. Older age was a risk factor for febrile neutropenia, occurring in 29% of patients who were age 65 or older versus 14% of patients less than age 65.

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

10 OVERDOSAGE

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

17 PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

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

Acute Pancreatitis: Advise patients to contact their health care provider if they develop severe abdominal pain.

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

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


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

Advise patients to report pregnancy immediately.

Lactation: Advise patients to avoid breastfeeding while receiving ADCETRIS.

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



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The ECHELON-2 Trial: Results of a Randomized, Double-Blind, Active-Controlled Phase 3 Study of Brentuximab Vedotin and CHP (A+CHP) Versus CHOP in the Frontline Treatment of Patients With CD30+ Peripheral T-Cell Lymphomas

Peripheral T-cell lymphoma (PTCL) refers to more than 2 dozen heterogeneous lymphoid malignancies that can be characterized as nodal, extranodal, leukemic, or cutaneous.¹ Standard first-line treatment is cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or a CHOP-like regimen, administered with curative intent.² However, outcomes in PTCL patients are generally poor, and the risk of relapse or progression is high.^{3,4} CD30 expression is universal among patients with systemic anaplastic large-cell lymphoma (sALCL).^{5,6} Across all PTCL subtypes, approximately 50% of patients' tumors express CD30.^{5,6} Brentuximab vedotin is an antibody-drug conjugate that is approved by the US Food and Drug Administration (FDA) for several indications, including the treatment of relapsed or refractory sALCL. Bren-

tuximab vedotin binds to CD30 and releases a cytotoxic agent, monomethyl auristatin E, into the cytoplasm after internalization. The cytotoxic agent disrupts microtubule assembly, leading to cell cycle arrest and apoptosis. Brentuximab vedotin was evaluated in combination with cyclophosphamide, doxorubicin, and prednisone (BV-CHP) in a phase 1 study of 26 patients with CD30-positive PTCL, including 19 patients with sALCL.⁷ The objective response rate (ORR) was 100%, with a complete response (CR) rate of 92%. After a median observation period of 59.6 months, neither the median progression-free survival (PFS) nor the median overall survival were reached. The estimated 5-year PFS was 52%. The combination was associated with a manageable toxicity profile.

The ECHELON-2 trial (A Comparison of Brentuximab Vedotin and

CHP With Standard-of-Care CHOP in the Treatment of Patients With CD30-Positive Mature T-Cell Lymphomas) compared BV-CHP vs CHOP as first-line treatment in patients with PTCL.⁸ The double-blind, double-dummy, international phase 3 trial enrolled patients with expression of CD30 in at least 10% of cells. Before randomization, patients were stratified based on their International Prognostic Index (IPI) score and histologic subtype. Patients received treatment every 3 weeks for 6 to 8 cycles. Patients in the BV-CHP arm received placebo vincristine and patients in the standard therapy arm received placebo brentuximab vedotin. Investigators could also add treatment with prophylactic granulocyte colony-stimulating factor, consolidation radiation therapy, or stem cell transplant (SCT). The primary endpoint was PFS by blinded independent central review according to Cheson 2007 criteria.⁹ The efficacy analysis included the intention-to-treat population. The safety analysis included all patients who received any amount of brentuximab vedotin or any component of CHOP therapy.

The trial enrolled 226 PTCL patients into each arm. Baseline characteristics were well-balanced between the 2 arms. Patients were a median age of 58 years (range, 18-85 years), 15% had an IPI score of 4 or 5, and 80.5% had stage III/IV disease. More than two-thirds of patients in each arm had sALCL. The planned treatment course of 6 or 8 cycles was completed by 88% of patients in the BV-CHP arm and 81% in the CHOP arm. Subsequent systemic therapy for residual or progressive disease was administered to 26% of patients in the

ABSTRACT SUMMARY: Excellent Outcome of Young Patients (18-60 Years) With Favorable-Prognosis Diffuse Large B-Cell Lymphoma Treated With 4 Cycles of CHOP Plus 6 Applications of Rituximab: Results of the 592 Patients of the FLYER Trial of the DSHNHL/GLA

The randomized international FLYER trial (Rituximab and Combination Chemotherapy in Treating Patients With Non-Hodgkin's Lymphoma) evaluated 6 cycles of R-CHOP or 4 cycles of R-CHOP plus 2 further cycles of rituximab for noninferiority in young, treatment-naive patients with aggressive B-cell lymphoma and a favorable risk profile (Abstract 781). Enrolled patients were ages 18 to 60 years and had stage I/II disease, an age-adjusted IPI of 0, and no lesions of 7.5 cm or larger. Among 588 patients, 79% had DLBCL. The trial achieved its primary endpoint, with a 3-year PFS of 94% with 6 cycles of R-CHOP vs 96% with 4 cycles of R-CHOP plus 2 cycles of rituximab alone. After a median follow-up of more than 5 years, the 3-year event-free survival was 89% in both arms. Overall survival was 98% with 6 cycles of R-CHOP vs 99% with 4 cycles of R-CHOP plus 2 cycles of rituximab. Rates of nonhematologic AEs were reduced by approximately one-third in patients who received 4 cycles of R-CHOP plus 2 cycles of rituximab alone.

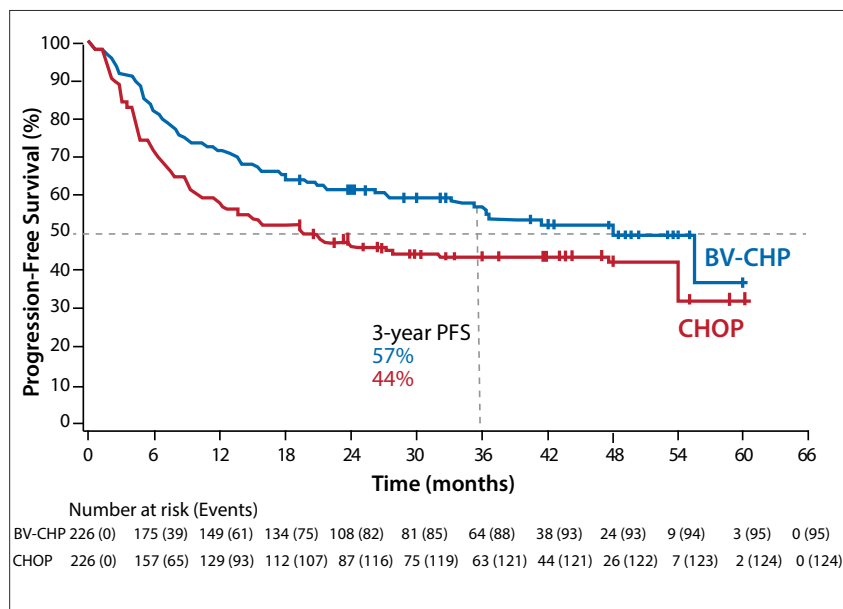


Figure 1. Estimated 3-year PFS with BV-CHP vs CHOP in the phase 3 ECHELON-2 study. BV-CHP, brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; ECHELON-2, A Comparison of Brentuximab Vedotin and CHP With Standard-of-Care CHOP in the Treatment of Patients With CD30-Positive Mature T-Cell Lymphomas; PFS, progression-free survival. Adapted from Horwitz SM et al. ASH abstract 997. *Blood*. 2018;132(suppl 1).⁸

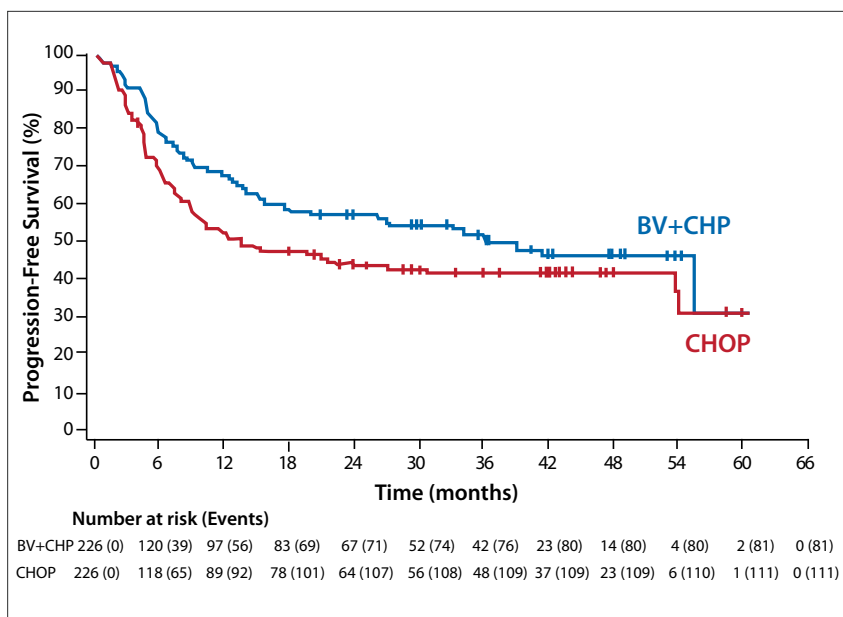


Figure 2. Progression-free survival with censoring at the time of consolidative stem cell transplant or radiation therapy among patients treated with BV-CHP or CHOP in the phase 3 ECHELON-2 study. BV-CHP, brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; ECHELON-2, A Comparison of Brentuximab Vedotin and CHP With Standard-of-Care CHOP in the Treatment of Patients With CD30-Positive Mature T-Cell Lymphomas. Adapted from Horwitz SM et al. ASH abstract 997. *Blood*. 2018;132(suppl 1).⁸

BV-CHP arm vs 42% of patients in the CHOP arm, and 4% of patients in each arm received palliative radiation treatment. Reasons for treatment discontinuation included progressive disease (3% in the BV-CHP arm vs 12% in the CHOP arm) and adverse events (AEs; in 7% of each arm).

After a median follow-up of 36.2 months, the median PFS was 48.2 months in the BV-CHP arm vs 20.8 months in the CHOP arm (hazard ratio [HR], 0.72; 95% CI, 0.54-0.93; $P=.011$). The estimated 3-year PFS was 57% with BV-CHP vs 44% with CHOP (Figure 1). After a median follow-up of 42.1 months, overall survival was also significantly improved with BV-CHP (not reached vs 17.5 months; HR, 0.66; 95% CI, 0.46-0.95; $P=.0244$). Based on prespecified analysis, treatment with BV-CHP yielded a favorable PFS vs CHOP in most subgroups, particularly patients with ALK-positive sALCL (HR, 0.29; 95% CI, 0.11-0.79), patients with an IPI score of 0 or 1 (HR, 0.53; 95% CI, 0.29-0.97), female patients (HR, 0.49; 95% CI, 0.31-0.78), and those with a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (HR, 0.66; 95% CI, 0.49-0.89). Prespecified subset analysis for overall survival showed a benefit for patients with ALK-negative sALCL (HR, 0.58; 95% CI, 0.35-0.98). However, most subgroups were too small for a statistical analysis with adequate power. PFS was analyzed with censoring at the time of consolidative SCT or radiation therapy and again showed a benefit among patients in the BV-CHP arm (HR, 0.71; 95% CI, 0.53-0.94; $P=.017$; Figure 2). A significant improvement with BV-CHP was also seen in other secondary endpoints, including the CR rate (68% vs 56%; $P=.0066$) and ORR (83% vs 72%; $P=.0032$). In the subset of patients with sALCL, the rate of subjects with a PFS event was 34% in the BV-CHP arm vs 48% in the CHOP arm (HR, 0.59; 95% CI, 0.42-0.84; $P=.0031$).

Rates of AEs were similar in both arms. AEs of grade 3 or higher occurred in 65% to 66% of patients overall. Rates of serious AEs were 38% to 39%, and the proportion of patients who died from AEs in the 2 arms was 3% to 4%. In the BV-CHP arm, the AE profile was consistent with the known safety profiles of brentuximab vedotin and CHOP chemotherapy. The rates of neutropenia of any grade were 49% in the BV-CHP arm vs 46% in the CHOP arm. The rates of febrile neutropenia of any grade were 20% vs 16%, respectively. Treatment-emergent peripheral neuropathy of any grade occurred in 117 patients in the BV-CHP arm vs 124 in the CHOP arm. All peripheral neuropathy events resolved in 50% and 64% of patients,

respectively. At the last follow-up, nearly all cases of peripheral neuropathy in both arms were grade 1/2.

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Rituximab/Bendamustine and Rituximab/Cytarabine Induction Chemotherapy for Transplant-Eligible Patients With Mantle Cell Lymphoma: A Pooled Analysis of Two Phase 2 Clinical Trials and Off-Trial Experience

A phase 2 trial conducted at the Dana-Farber Cancer Institute evaluated 3 cycles of rituximab/bendamustine followed by 3 cycles of rituximab/cytarabine prior to autologous SCT.^{1,2} The rituximab/bendamustine regimen consisted of rituximab at 375 mg/m² on day 1 plus bendamustine at 90 mg/m² on days 1 and 2. The rituximab/cytarabine regimen consisted of rituximab at 375 mg/m² on day 1 plus cytarabine at 3 g/m² twice daily on days 1 and 2. The trial enrolled 23 treatment-naïve mantle cell lymphoma patients between 2012 and 2014. The patients' age ranged from 42 years to 69 years, and 70% had a mantle cell lymphoma IPI (MIPI) score indicating low-risk disease. The trial's primary endpoint was the CR rate after 6 cycles of therapy, with a goal of achieving a

CR rate of at least 75%. The rate of CR/unconfirmed CR was 96%. After a median follow-up of 13 months, the PFS rate was 96%. Additional patients at the Dana-Farber Cancer Institute received the same induction therapy followed by autologous SCT. From 2016 to 2018, a phase 2 clinical trial at Washington University in St Louis also evaluated rituximab/bendamustine and rituximab/cytarabine, but with a different treatment course. Patients received rituximab/bendamustine during cycles 1, 3, and 5, plus rituximab/cytarabine during cycles 2, 4, and 6, followed by autologous SCT.

To gain a better understanding of the efficacy and safety of these regimens, a pooled analysis was conducted including patients from the 2 clinical trials and patients who were

treated off-study at the Dana-Farber Cancer Institute.⁵ Both phase 2 clinical trials included patients with treatment-naïve mantle cell lymphoma who had adequate organ function and an ECOG performance status of 0 to 2. Patients who were treated outside of a clinical trial at Dana-Farber were identified retrospectively and included adults with treatment-naïve mantle cell lymphoma treated with rituximab/bendamustine and rituximab/cytarabine before undergoing autologous SCT. The analysis included 23 patients from the Dana-Farber Cancer Institute trial, 49 patients who were treated at Dana-Farber outside of a clinical trial, and 14 patients treated as part of the Washington University trial. Among all patients included in the analysis, the median age was

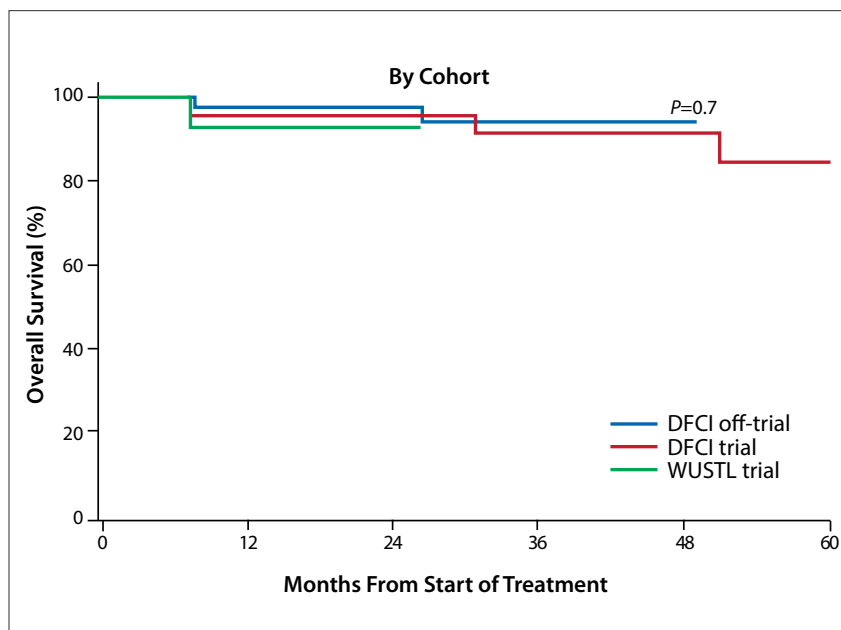


Figure 3. Overall survival according to patient cohort among transplant-eligible patients with mantle cell lymphoma who received induction treatment with rituximab/bendamustine or rituximab/cytarabine. DFCI, Dana-Farber Cancer Institute; WUSTL, Washington University in St Louis. Adapted from Merryman RW et al. ASH abstract 145. *Blood*. 2018;132(suppl 1).¹

57 years (range, 30-72 years), and 72% were male. Stage III/IV disease was reported in 97% of patients, and 97% had an ECOG performance status of 0 or 1.

Eighty percent of patients were treated at an academic treatment center, and the remainder were treated at a community treatment center. The Ki67 level was between 0% and 30% in 53% of patients, and exceeded 30% in 26% of patients. (The level was not available for 21% of patients.) The MIPI score was low in 57%, intermediate in 20%, high in 15%, and not reported in 8% of patients in the entire study population. In the Washington University trial, 43% of patients had a high MIPI score. Blastoid mantle cell lymphoma was seen in 13% of patients overall, including 29% of patients treated in the Washington University trial, 14% treated at the Dana-Farber Cancer Institute

outside of a clinical trial, and 0% in the Dana-Farber trial. More than 90% of patients in each cohort completed all 6 treatment cycles. The starting dose of cytarabine was 3 g/m² in 61% of patients in the Dana-Farber Cancer Institute trial, 8% of patients treated off-trial at Dana-Farber, and 64% of patients treated in the Washington University trial. After induction treatment, the ORR was 96% (22/23) in the Dana-Farber phase 2 trial, 100% (49/49) in patients treated off-trial at Dana-Farber, and 93% (13/14) in patients in the Washington University phase 2 trial. CR rates were 96% (22/23), 94% (46/49), and 79% (11/14), respectively.

Among 86 patients overall, 81 (94%) completed 6 cycles of induction therapy. After induction therapy, 77 patients proceeded to autologous SCT. One of these patients died from respiratory failure and Rous

sarcoma virus infection on day 56 after SCT, and the death was considered treatment-related. Delayed platelet engraftment was more likely among patients who were treated with cytarabine at 3 g/m² vs patients treated with a lower dose of cytarabine, as well as in patients treated with alternating rituximab/bendamustine and rituximab/cytarabine vs those treated with 3 sequential cycles of each therapy ($P < .05$). After a median follow-up of 32 months, the estimated 3-year PFS was 85% (95% CI, 74%-92%), and the estimated 5-year PFS was 80% (95% CI, 66%-89%). Predictors of PFS included the MIPI score and the diagnosis of blastoid or pleomorphic mantle cell lymphoma. The estimated 3-year overall survival was 92% (95% CI, 81%-97%), and the estimated 5-year overall survival was 85% (95% CI, 62%-95%). Overall survival according to the patient cohort is shown in Figure 3.

No treatment-related deaths were reported during induction therapy. Five patients discontinued therapy, for reasons including persistent cytopenias (n=3), grade 3 rash associated with bendamustine (n=1), and progressive disease (n=1). As expected, grade 3/4 hematologic AEs were common, affecting the majority of patients. The most common grade 4 hematologic AEs were lymphopenia (92%), thrombocytopenia (81%), and leukopenia (78%). Grade 3/4 nonhematologic AEs were not common, with the exception of febrile neutropenia (16%).

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Nivolumab Combined With Brentuximab Vedotin for Relapsed/Refractory Primary Mediastinal Large B-Cell Lymphoma: Preliminary Results From the Phase 2 CheckMate 436 Trial

The combination of nivolumab plus brentuximab vedotin has shown synergistic antitumor activity in hematologic malignancies, such as classical Hodgkin lymphoma.¹ The phase 1/2 CheckMate 436 trial (An Investigational Immuno-Therapy Safety and Effectiveness Study of Nivolumab in Combination With Brentuximab Vedotin to Treat Non-Hodgkin Lymphomas) is an open-label, single-arm, dose-finding, cohort-expansion study that is evaluating the combination of nivolumab and brentuximab vedotin in patients with relapsed/refractory non-Hodgkin lymphoma (NHL), peripheral T-cell lymphoma, diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma, mediastinal gray zone lymphoma, and cutaneous T-cell lymphoma (mycosis fungoides/Sézary syndrome). Dr Alison Moskowitz presented preliminary data for 30 patients with relapsed or refractory primary mediastinal large B-cell lymphoma treated in the expansion phase.²

The patients' median age was 35.5 years (range, 19-83 years). Nearly all patients (97%) were younger than 65 years. Refractory disease was reported in 60%, relapsed disease in 23%, and relapsed/refractory disease in 17%. Patients had an ECOG performance status of 0 (63%) or 1 (37%). At initial diagnosis, the disease stage was 1 in 13%, 2 in 40%, 3 in 7%, and 4 in 37%. (Disease stage was unknown in 3% of patients.) The number of prior lines of systemic therapy was 2 in 60% and 3 or more in 37%. Patients received nivolumab at 240 mg on day 1 plus brentuximab vedotin at 1.8 mg/kg on day 1 in 21-day cycles until disease progression or unacceptable toxicity.

The investigator-assessed ORR was 70% (95% CI, 51%-85%), includ-

ing a CR rate of 27% and a partial response rate of 43%. In 14 patients, the best reduction in target lesion volume was 50% or higher (Figure 4). The median time to response was 1.3 months (range, 1.1-4.8 months), and the median time to CR was 3.0 months (range, 1.2-6.9 months; Figure 5). The median duration of response and duration of CR were not reached.

After a median follow-up of 6.1 months, 33% of patients were still receiving treatment. The most common reasons for treatment discontinuation included achievement of maximum clinical benefit according to the investigator (30%), disease progression (23%), and an adverse event unrelated to the study drug (7%). Patients received a median of 5.0 doses of nivolumab and 4.5 doses of brentuximab vedotin.

Treatment-related AEs occurred

in 83% of patients. The most common grade 3/4 AEs were neutropenia (27%), thrombocytopenia (7%), and decreased neutrophil count (7%). Three patients (10%) had treatment-related serious AEs, including a grade 5 acute kidney injury. The rate of infusion reactions was less than 5%. No patient in either treatment group required a transfusion interruption. Treatment was discontinued owing to 2 AEs: grade 3/4 disease progression and grade 5 sepsis. At the time of the study report, 4 patients had died.

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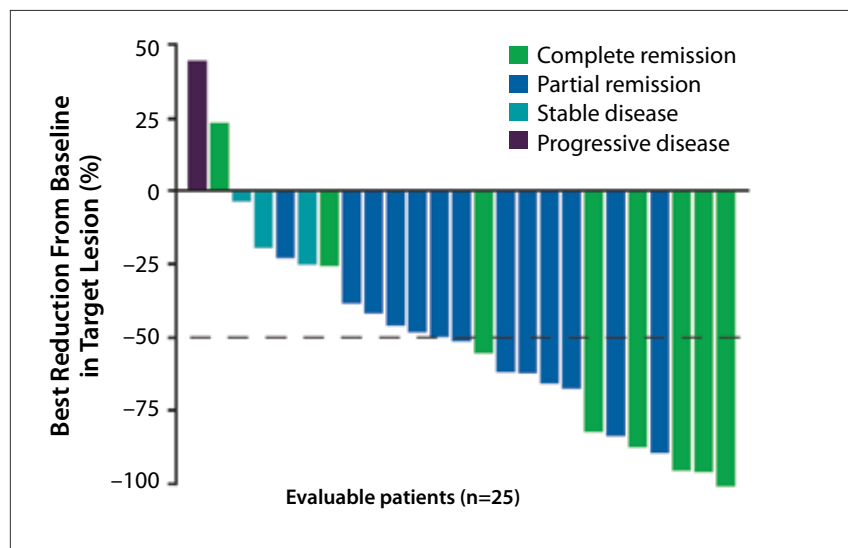


Figure 4. The best reduction in target lesion volume from baseline among patients with relapsed/refractory primary mediastinal large B-cell lymphoma treated with nivolumab plus brentuximab vedotin in the phase 2 CheckMate 436 trial. CheckMate 436, An Investigational Immuno-Therapy Safety and Effectiveness Study of Nivolumab in Combination With Brentuximab Vedotin to Treat Non-Hodgkin Lymphomas. Adapted from Moskowitz AJ et al. ASH abstract 1691. *Blood*. 2018;132(suppl 1).²

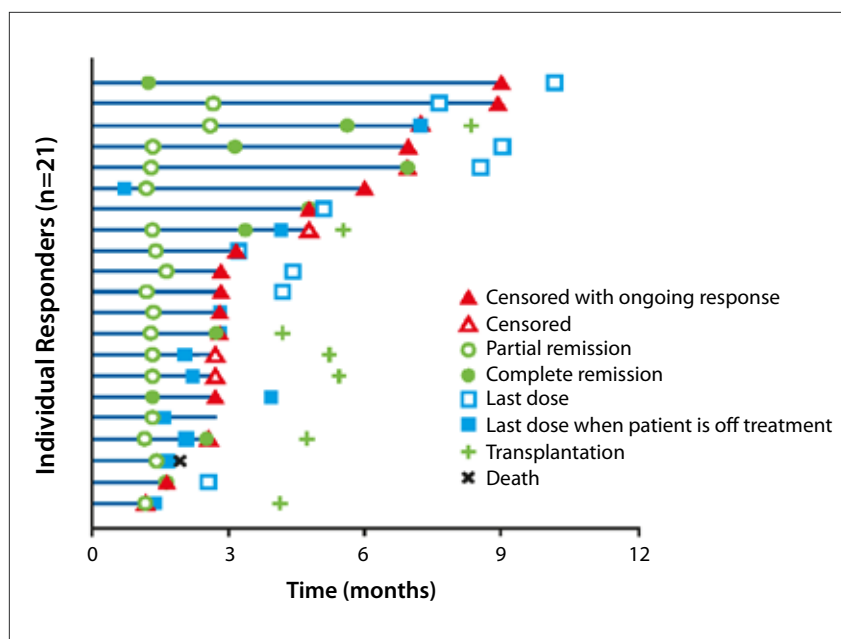


Figure 5. Time to and durability of responses in the phase 2 CheckMate 436 trial of nivolumab combined with brentuximab vedotin for relapsed/refractory primary mediastinal large B-cell lymphoma. CheckMate 436, An Investigational Immuno-Therapy Safety and Effectiveness Study of Nivolumab in Combination With Brentuximab Vedotin to Treat Non-Hodgkin Lymphomas. Adapted from Moskowitz AJ et al. ASH abstract 1691. *Blood*. 2018;132(suppl 1).²

Axicabtagene Ciloleucel CD19 Chimeric Antigen Receptor (CAR) T-Cell Therapy for Relapsed/Refractory Large B-Cell Lymphoma: Real World Experience

Axicabtagene ciloleucel is a CD19-directed chimeric antigen receptor (CAR) autologous T-cell therapy.¹ After apheresis, the patient's T cells are engineered to express the single-chain extracellular variable domain that targets CD19, with CD3 ζ and CD28 intracellular domains for T-cell activation. Axicabtagene ciloleucel is approved in the United States for treatment of adults with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy. In the phase 1/2 ZUMA-1 trial (Safety and Efficacy of KTE-C19 in Adults With Refractory Aggressive Non-Hodgkin Lymphoma), 108 patients with histologically confirmed large B-cell lymphoma received conditioning chemotherapy followed by infusion with axicabtagene ciloleucel.² The ORR was 82%, with a CR rate of 58%. After a median follow-up of 15.4 months, 42% of patients continued to have a response.

Real-world experience with axicabtagene ciloleucel was evaluated in a retrospective analysis of patients from 17 treatment centers who received treatment as the standard of care based on the FDA label.³ Among the 295 patients who underwent leukapheresis, the product did not meet specifications for 7 patients, 12 patients died from causes secondary to lymphoma, 1 patient developed infection, and 1 patient had nonmeasurable disease. The median time to the start of conditioning chemotherapy after leukapheresis was 21.5 days. After leukapheresis and before administration of conditioning treatment, 158 patients received bridging therapy, including chemotherapy (56%), corticosteroids (24%), and radiation therapy (13%). Conditioning chemotherapy consisting of cyclophosphamide (500 mg/m²) plus fludarabine (30 mg/m²) for 3 days was administered to 274 patients. All of the patients who received

conditioning chemotherapy proceeded to axicabtagene ciloleucel at 2×10^6 CAR T cells/kg.

The patients' median age was 60 years (range, 21-83 years), one-third were ages 65 years or older, and 65% were male. Two-thirds of patients had DLBCL, including 6% with transformed follicular lymphoma and 26% with primary mediastinal B-cell lymphoma. An ECOG performance status of 0 or 1 was reported in 81%, and 84% had stage III/IV disease. Fifty-five percent of patients had an IPI score of 3 or higher. Seventy-five percent of patients had received 4 or more prior therapies, and 33% had relapsed after autologous SCT. Among patients with DLBCL, 151 (60%) had the germinal center B-cell (GCB) subtype and 102 (40%) had the activated B-cell (ABC) subtype. Sixty-two DLBCL patients (23%) had double- or triple-hit genetics based on fluorescence in situ hybridization, and

ABSTRACT SUMMARY B-CAP (Brentuximab Vedotin, Cyclophosphamide, Doxorubicin and Predniso[lo]ne) in Older Patients With Advanced-Stage Hodgkin Lymphoma: Results of a Phase II Intergroup Trial By the German Hodgkin Study Group and the Nordic Lymphoma Group

A phase 2 trial investigated the feasibility of brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisone/prednisolone (B-CAP) for the treatment of elderly patients with advanced-stage HL (Abstract 926).¹ Patients were ages 60 years or older and had histologically proven, classical HL. The 49 patients were a median age of 66 years (range, 60-84 years), and 47% were female. One patient died before interim staging after treatment cycle 2. Among 48 evaluable patients, the rate of CR/unconfirmed CR was 44% and the partial response rate was 54%, yielding an ORR of 98%, with a lower confidence limit of 90.5%. Based on PET imaging, the metabolic CR rate was 65%. After a median observation time of 15 months, 29% of patients experienced a PFS event. The estimated 1-year PFS was 73.9% (95% CI, 61.1%-86.6%). The most common grade 3/4 hematologic toxicities were neutropenia (53%) and leukopenia (53%).

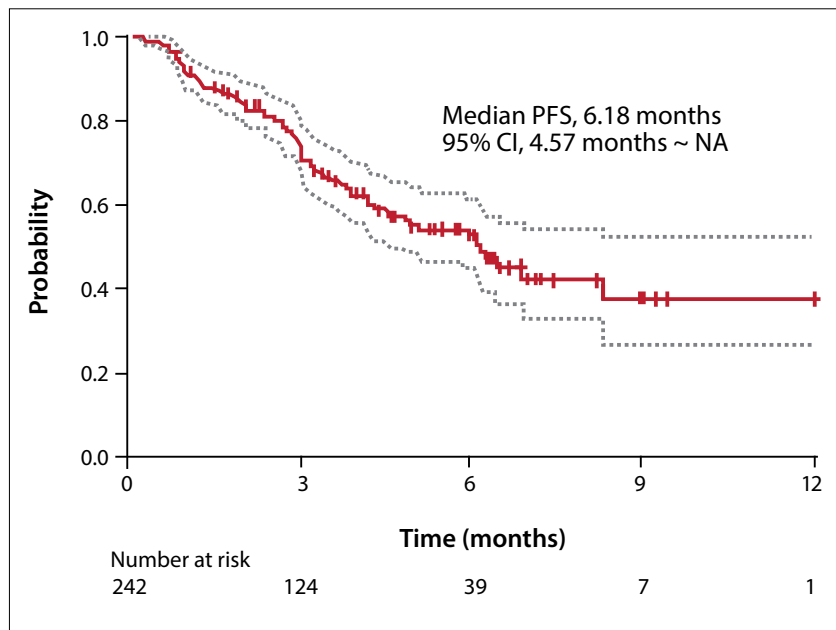


Figure 6. Median PFS in a real-world analysis of patients with relapsed/refractory large B-cell lymphoma treated with axicabtagene ciloleucel. PFS, progression-free survival. Adapted from Nastoupil LJ et al. ASH abstract 91. *Blood*. 2018;132(suppl 1).³

38% had double-expressor genetics. Forty-three percent of patients treated in the real-world study did not meet the eligibility requirements for inclusion in the ZUMA-1 trial at the time of leukapheresis, based

on an inadequate platelet count (13%), active deep vein thrombosis/pulmonary embolism (9%), prior CD19 or CAR T-cell therapy (8%), inadequate glomerular filtration rate (8%), history of central nervous sys-

tem lymphoma (8%), symptomatic pleural effusion (4%), left ventricular ejection fraction (4%), and prior allogeneic SCT (2%).

The 30-day ORR in 238 patients was 80%, including a CR rate of 47%. The 90-day ORR in 248 patients was 81%, including a CR rate of 57%. In 153 evaluable patients with an ongoing CR at 3 months, covariate analysis showed no significant differences in the CR rate in subgroups based on age, disease subtype, cell of origin, double- or triple-hit genetics, IPI score, use of bridging therapy, use of tocilizumab or corticosteroids, or admission to an intensive care unit. Covariates that were associated with the likelihood of a CR included female sex ($P=.009$), an ECOG performance status of 1 or 2 ($P=.024$), relapsed disease ($P=.011$), nonbulky disease ($P=.040$), and meeting all of the eligibility requirements for the ZUMA-1 trial ($P=.037$). After a median follow-up of 3.9 months, the median PFS was 6.18 months (95% CI, 4.57 months to not evaluable; Figure 6), and the estimated 6-month overall survival was 72% (95% CI, 65%-80%).

Any-grade cytokine release syndrome occurred in 92% of patients; the syndrome was grade 3 or higher in 7%. The median time to onset of cytokine release syndrome was 3 days. Neurotoxicity of any grade occurred in 69% of patients, and was grade 3 or higher in 33%. The median time to onset of neurotoxicity was 6 days. Tocilizumab was administered to 63% of patients, and corticosteroids to 55%. The median hospital stay was 14 days, and 32% of patients required admission to the intensive care unit. Three patients experienced a grade 5 AE, and treatment-related deaths occurred in 1% of patients. After axicabtagene ciloleucel treatment, 7 patients died from nonrelapse events that included infection ($n=5$), hemophagocytic lymphohistiocytosis ($n=1$), and cerebral edema ($n=1$).

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Venetoclax Plus Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone (R-CHOP) Improves Outcomes in BCL2-Positive First-Line Diffuse Large B-Cell Lymphoma: First Safety, Efficacy, and Biomarker Analyses From the Phase II CAVALLI Study

The single-arm, phase 1/2 CAVALLI study (A Safety and Pharmacokinetics [PK] Study of Venetoclax in Participants With Non-Hodgkin's Lymphoma) investigated the combination of venetoclax, a BCL-2 inhibitor, plus rituximab plus CHOP (R-CHOP) as first-line therapy in DLBCL patients.¹ The trial enrolled adults with an IPI of 2 to 5, an ECOG performance status of 0 to 2, and at least 1 measurable lesion exceeding 1.5 cm. Patients received venetoclax at 800 mg on days 4 to 10 of cycle 1 and on days 1 to 10 during cycles 2 to 8. Rituximab at 375 mg/m² was administered on day 1 of all 8 cycles, and patients also received 6 cycles of CHOP. The primary endpoint was the CR rate by independent review of positron emission tomography (PET) results at the end of treatment, using modified Lugano criteria.² The historical control was drawn from results from DLBCL patients with an IPI of 2 to 5 who received R-CHOP in the GOYA trial (A Study of Obinutuzumab in Combination With CHOP Chemotherapy Versus Rituximab With CHOP in Participants With CD20-Positive Diffuse Large B-Cell Lymphoma) because R-CHOP represents the current standard of care.³ Levels of BCL-2 and MYC expression were assessed by immunohistochemistry using validated assays. BCL-2 positivity was defined as at least 50% of tumor cells showing moderate or strong staining intensity. BCL-2 and

MYC translocations were assessed by fluorescence in situ hybridization.

The CAVALLI trial enrolled 208 patients, whose median age was 65 years (range, 18-85 years).¹ Forty-five percent of patients were female, and 84% had an ECOG performance status of 0 or 1. Eighty-four percent of patients had stage III/IV disease, and one-fourth of patients had an IPI score of 4 or 5. The 564 patients from the GOYA trial had a median age of 62 years (range, 18-83 years), and 47% were female. Eighty-five percent of patients had an ECOG performance status of 0 or 1, and 85% had stage III/IV disease. Nineteen percent of patients had an IPI score of 4 to 5.

The PET-CR rate by independent review was 69% with venetoclax plus

R-CHOP vs 63% with R-CHOP, representing a difference of 6% (95% CI, 0%-13%). The addition of venetoclax improved the PET-CR rate in patients with BCL-2-positive disease according to immunohistochemistry (65% vs 60%) and fluorescence in situ hybridization (70% vs 48%). Seven patients in the CAVALLI trial and 8 in the GOYA trial had double-hit genetics, with both BCL-2 and MYC translocation. In these patients, the inclusion of venetoclax yielded the most dramatic increase in the PET-CR rate (71% vs 25%). After a median follow-up of 22.3 months for CAVALLI patients and 29.6 months for GOYA patients, the addition of venetoclax to R-CHOP yielded a superior PFS (Table 1). A PFS benefit was observed with the addition

Table 1. PFS Benefit in Patients From the CAVALLI and GOYA Trials

| Population | HR for PFS (95% CI) | |
|----------------------------|---------------------|--------------------------|
| | Unadjusted | Adjusted for Covariates* |
| Overall | 0.64 (0.45-0.90) | 0.6 (0.41-0.87) |
| BCL-2 IHC-positive | 0.60 (0.37-0.98) | 0.58 (0.35-0.97) |
| BCL-2 FISH-positive | 0.54 (0.25-1.2) | 0.64 (0.29-1.4) |
| BCL-2/MYC double-expressor | 0.75 (0.45-1.3) | 0.78 (0.45-1.3) |

*Covariates included age, sex, ECOG performance status, body mass index, International Prognostic Index, bulky disease, disease stage, lactate dehydrogenase levels, and cell of origin.

CAVALLI, A Safety and Pharmacokinetics [PK] Study of Venetoclax in Participants With Non-Hodgkin's Lymphoma; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; GOYA, A Study of Obinutuzumab in Combination With CHOP Chemotherapy Versus Rituximab With CHOP in Participants With CD20-Positive Diffuse Large B-Cell Lymphoma; HR, hazard ratio; IHC, immunohistochemistry; PFS, progression-free survival.

Data from Morchhauser F et al. ASH abstract 782. *Blood*. 2018;132(suppl 1).¹

of venetoclax to R-CHOP among patients with BCL-2 expression in the ABC subtype (HR, 0.42; 95% CI, 0.19-0.93) and the GCB subtype (HR, 0.55; 95% CI, 0.26-1.2). The HR for overall survival was 0.67 (95% CI, 0.43-1.1) for the entire study population and 0.65 (95% CI, 0.35-1.2) for patients with *BCL-2*-positive disease by immunohistochemistry, suggesting a possible survival benefit with the addition of venetoclax to R-CHOP.

In the CAVALLI study, 61% of patients received venetoclax at a dose intensity exceeding 90%. Dose intensities for cyclophosphamide, doxorubicin, and vincristine were similar in the CAVALLI and GOYA trials, with between 70% and 76% of patients in both arms receiving more than 90% dose intensity for each agent.

Grade 5 AEs occurred in 2% of patients in the CAVALLI trial and 5% in the GOYA trial. Serious AEs were observed in 56% vs 41%, respectively, and grade 3/4 AEs occurred in 86% vs 66%. AEs leading to withdrawal of any treatment were also more common in the CAVALLI trial, at 24% vs 10%. In the CAVALLI trial, 20% of these events were caused by venetoclax toxicity. Grade 3/4 cytopenia was more common in the population treated with venetoclax. Febrile neutropenia was observed in 31% of patients in the

ABSTRACT SUMMARY: A Global, Randomized, Placebo-Controlled, Phase 3 Study of Ibrutinib Plus Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in Patients With Previously Untreated Non-Germinal Center B-Cell-Like Diffuse Large B-Cell Lymphoma

A randomized, placebo-controlled phase 3 study investigated the impact of ibrutinib at 560 mg daily added to R-CHOP in patients with treatment-naïve, non-GCB-type DLBCL (Abstract 784). More than 40% of patients were older than 65 years, and approximately three-fourths of patients had stage III/IV disease. The median follow-up was 34.8 months. In the overall population of 838 patients, event-free survival was similar for both arms (HR, 0.934; 95% CI, 0.726-1.200; $P=.5906$). Event-free survival was also similar for the subset of 567 patients with ABC-type DLBCL in both arms (HR, 0.949; 95% CI, 0.704-1.279; $P=.7311$). However, in the 342 patients younger than 60 years, event-free survival was superior with the addition of ibrutinib (HR, 0.579; 95% CI, 0.380-0.881), as was overall survival (HR, 0.330; 95% CI, 0.162-0.673). In older patients, the addition of ibrutinib to R-CHOP was associated with increased rates of serious AEs and AEs leading to treatment discontinuation.

CAVALLI trial vs 16% of patients in the GOYA trial.

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Response-Adapted Therapy With Nivolumab and Brentuximab Vedotin (BV), Followed By BV and Bendamustine for Suboptimal Response, in Children, Adolescents, and Young Adults With Standard-Risk Relapsed/Refractory Classical Hodgkin Lymphoma

Hodgkin lymphoma (HL) is the most common cancer in children, adolescents, and young adults. For young patients with relapsed or refractory HL, autologous SCT is the standard of care. However, in a small prospective study of young patients with relapsed or refrac-

tory HL, the 5-year probability of failure-free survival was only 31% after high-dose chemotherapy followed by autologous SCT.¹ Based on functional PET imaging before autologous SCT, HL patients who achieved a metabolic CR had a 5-year event-free survival of 75%, whereas patients with PET-

positive disease had a 5-year event-free survival of 31%.² Similarly, in a study of pediatric HL patients, multivariate analysis showed that PFS was prolonged in those with a Karnofsky/Lansky score of at least 90, no extranodal involvement, and chemosensitive disease.³ New treatment strategies

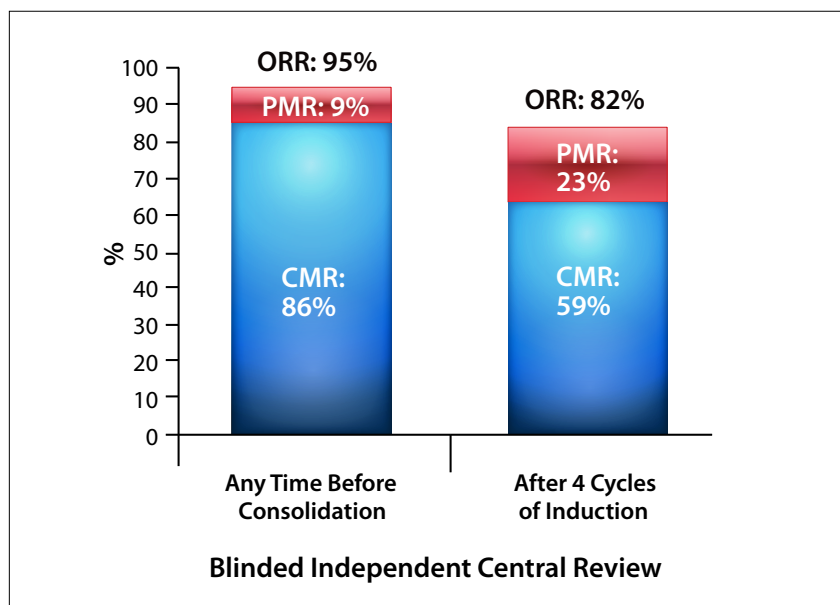


Figure 7. The rate of metabolic complete response prior to consolidation based on blinded independent central review in a study of nivolumab and brentuximab vedotin, followed by brentuximab vedotin and bendamustine, in young patients with standard-risk relapsed/refractory classical Hodgkin lymphoma. CMR, complete metabolic response; ORR, overall response rate; PMR, partial metabolic response. Adapted from Harker-Murray PD et al. ASH abstract 927. *Blood*. 2018;132(suppl 1).⁵

should be optimized to provide high rates of metabolic CR while limiting long-term toxicity. Response-based therapy may provide a methodology for optimizing treatment of young HL patients by providing the most effective and least toxic approach.⁴

The open-label CheckMate 744 trial (A Study of Nivolumab Plus Brentuximab Vedotin in Patients Between 5 and 30 Years Old, With Hodgkin's Lymphoma [cHL], Relapsed or Refractory From First Line Treatment) investigated 4 cycles of brentuximab vedotin plus nivolumab followed by 4 cycles of brentuximab vedotin plus bendamustine.⁵ The combined treatments were chosen based on results that showed an ORR of 82% with brentuximab vedotin plus nivolumab and an ORR of 92% with brentuximab vedotin plus bendamustine as salvage treatment in adult HL patients with relapsed or refractory disease.^{6,7} CheckMate 744 enrolled patients with classical CD30-positive HL, ages 5 to 30 years, who

had relapsed after or were refractory to their first line of therapy. Patients had a Karnofsky or Lansky performance status of at least 50. Prior treatment with brentuximab vedotin was permitted. Exclusion criteria included prior treatment with a checkpoint inhibitor or bendamustine, prior SCT, autoimmune disease, or immunodeficiency. Stratification to the standard-risk cohort was based on the presence of refractory disease or early relapse after treatment, the presence of B symptoms or extranodal disease, relapse in a prior radiation field, extensive disease with radiation therapy contraindicated, or stage IIIB or IV disease at initial diagnosis. After every 2 treatment cycles, patients were evaluated for metabolic response. Induction treatment consisted of 4 cycles of brentuximab vedotin plus nivolumab. Patients with a metabolic partial response after cycle 4 received intensive treatment by means of an additional 2 or 4 cycles of brentuximab vedotin plus bendamustine. Patients

who achieved a metabolic CR after 4, 6, or 8 cycles of treatment proceeded to high-dose chemotherapy and autologous SCT.

The standard-risk cohort included 44 patients with a median age of 16 years (range, 9-30 years). Sixty-six percent of patients were male. The median performance status score was 100, and 52% of patients had stage III/IV disease at diagnosis. Fifty-five percent of patients had primary refractory disease, and 32% of patients had relapsed between 3 and 11 months after their first line of therapy. Forty-three percent of patients had B symptoms or extranodal involvement at relapse, and 11% had bone marrow involvement.

Among the 42 patients who completed induction treatment, 23 proceeded to consolidation with high-dose chemotherapy and autologous SCT after 4 cycles of brentuximab vedotin plus nivolumab. Eleven patients proceeded to intensification treatment with brentuximab vedotin plus bendamustine, and 9 of these patients completed intensification therapy. Eight of these patients then proceeded to consolidation. Among the 31 patients who underwent autologous SCT, 30 completed consolidation treatment. Based on blinded independent central review, a metabolic CR was achieved by 86% (38/44) of patients prior to consolidation (Figure 7). After 4 cycles of induction treatment, the ORR was 82% and included a 59% metabolic CR rate. Subgroup analysis revealed metabolic CR rates of 83% to 100% in subgroups based on age and response to first-line therapy.

Grade 3/4 treatment-related AEs were observed in 18% of patients during induction and in 27% of patients during intensification. During induction therapy, the most common non-hematologic AEs of any grade related to treatment were nausea (18%), hypersensitivity (16%), and diarrhea (14%). During intensification, the most common events were vomiting (55%), nausea (36%), and headache

(18%). Rates of hematologic AEs were low. There were no reports of febrile neutropenia, thrombocytopenia, anemia, or decreased lymphocyte count in either phase. Treatment-related, grade 1 peripheral sensory neuropathy occurred in 1 patient during induction. Treatment-related serious AEs included hypersensitivity in 2 patients, and anaphylactic reaction, organizing pneumonia, pulmonary veno-occlusive disease, infusion-related reaction, and prolonged activated partial thromboplastin time, each occurring in 1 patient. There were few treatment-

related immune-mediated AEs, and none led to discontinuation.

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

The phase 1/2 E4412 trial investigated the hypothesis that releasing immune checkpoint blockades while simultaneously targeting cells via CD30-directed toxicity could overcome tumor resistance.¹ The report at the 60th American Society of Hematology meeting included patients in arms G through I. Patients in arm G received the starting dose of ipilimumab at 1 mg/kg on day 1, every 12 weeks for 2 years; nivolumab at 3 mg/kg on day 1 of cycles 1 through 46; and brentuximab vedotin at 1.2 mg/kg on day 1 of cycles 1 through 16. Patients in arm H received the same ipilimumab and nivolumab regimens plus brentuximab vedotin at 1.8 mg/kg on day 1 of cycles 1 through 16. Arm I was the expansion cohort, and these patients received the same regimen as in arm H. All treatment cycles were 21 days.

Eligible patients were adults with relapsed or refractory HL with measurable disease and a performance status of 0 to 2 according to criteria from ECOG/American College of

Radiology Imaging Network. Exclusion treatment included any prior treatment with nivolumab. Patients could have received prior brentuximab vedotin within 6 months before registration, but the study excluded patients who relapsed within 6

months after treatment. The trial enrolled 22 patients with relapsed HL. The patients' median age was 35 years (range, 19-60 years), and 50% were female. All patients had a baseline ECOG performance status of 0 or 1. The median number of prior

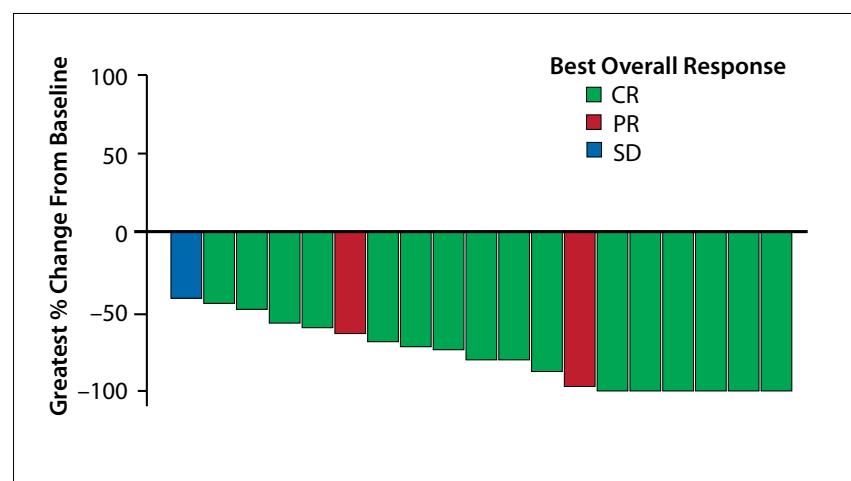


Figure 8. Best overall responses in a phase 1 study of ipilimumab, nivolumab, and brentuximab vedotin in patients with relapsed/refractory Hodgkin lymphoma. CR, complete response; PR, partial response; SD, stable disease. Adapted from Diefenbach C et al. ASH abstract 679. *Blood*. 2018;132(suppl 1).¹

systemic therapies was 2 (range, 1-5). Forty-one percent of patients had undergone prior SCT, and 5% had received prior treatment with brentuximab vedotin.

Among 22 patients in the 3 arms, the ORR was 82%, with a CR rate of 72%. One patient had stable disease, and 3 patients were not evaluable. Best overall responses are shown in Figure 8. Among the 19 patients who were treated with at least 3 cycles of study therapy and who had at least

1 disease assessment, the ORR was 95%, with a CR rate of 84%. After a median follow-up of 9 months, the median PFS was not reached. After a median follow-up of 1 year, median overall survival was not reached.

The most common AEs of any grade were nausea, fatigue, and diarrhea. Grade 3 fatigue, maculopapular rash, and vomiting occurred in 2 patients each.

Study E4412 is open for recruitment and will randomly assign

patients to arms K and L. Patients will receive nivolumab plus brentuximab vedotin, with or without ipilimumab.

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Brentuximab Vedotin Plus Chemotherapy in Patients With Advanced-Stage Classical Hodgkin Lymphoma: Evaluation of Modified Progression-Free Survival and Traditional PFS in the Phase 3 ECHELON-1 Study

The open-label, multicenter, randomized phase 3 ECHELON-1 trial (A Frontline Therapy Trial in Participants With Advanced Classical Hodgkin Lymphoma) evaluated brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (BV-AVD) vs AVD plus bleomycin (ABVD) in 1334 patients with treatment-naïve, advanced classical HL.¹ To account for the impact of subsequent treatment on efficacy outcomes, the primary endpoint was modified PFS (mPFS) by independent review, with mPFS events defined as disease progression, death, or subsequent chemotherapy and/or radiation therapy following a partial response or less after completion of study treatment. After a median follow-up of 24.6 months, mPFS was 82.1% in patients treated with BV-AVD vs 77.2% in those treated with ABVD (HR, 0.77; 95% CI, 0.60-0.98; $P=.035$; Figure 9).

Additional prespecified analyses were conducted to determine how treatment with subsequent therapy affected efficacy in ECHELON-1.²

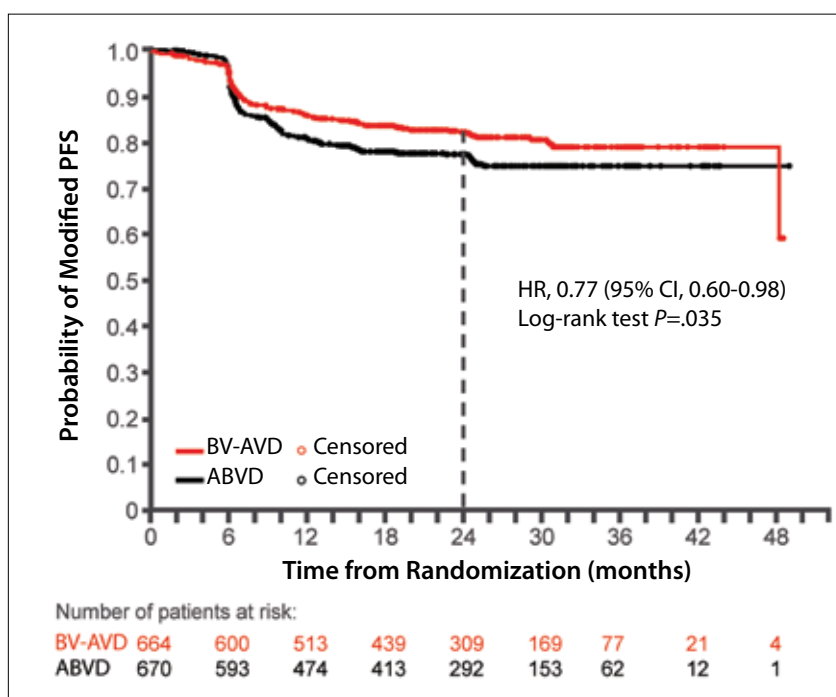


Figure 9. Modified PFS in patients treated with BV-AVD or ABVD in the phase 3 ECHELON-1 study. ABVD, doxorubicin, vinblastine, and dacarbazine plus bleomycin; BV-AVD, brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ECHELON-1, A Frontline Therapy Trial in Participants With Advanced Classical Hodgkin Lymphoma; HR, hazard ratio; PFS, progression-free survival. Adapted from Connors JM et al. ASH abstract 2904. *Blood*. 2018;132(suppl 1).²

The 2-year mPFS based on investigator assessment was 81.0% with BV-AVD vs 74.4% with ABVD (HR, 0.72; 95% CI, 0.57-0.91; $P=.006$). The inclusion of chemotherapy, but not radiation therapy, as a PFS event showed an investigator-assessed PFS benefit with BV-AVD vs ABVD (84.0% vs 77.3%; HR, 0.69; 95% CI, 0.53-0.89; $P=.003$). Standard, investigator-assessed PFS, with PFS events defined as disease progression or death, was 84.2% with BV-AVD vs 78.0% with ABVD (HR, 0.70; 95% CI, 0.54-0.91; $P=.006$). After a median of 37.1 months of follow-up, a post hoc analysis showed that the benefit of BV-AVD was maintained based on investigator-assessed PFS, at

83.1% vs 76.0% (HR, 0.70; 95% CI, 0.55-0.90; $P=.005$).

Further analyses were conducted to evaluate investigator-assessed PFS in subgroups based on PET results after treatment cycle 2 (PET2) and age. In patients with a negative PET2 result, the estimated 3-year PFS was superior with BV-AVD vs ABVD ($P=.005$). In patients with a positive PET2 result, BV-AVD was superior, but the results did not reach significance ($P=.077$). Patients younger than 60 years had a significant investigator-assessed PFS benefit with BV-AVD compared with ABVD ($P=.008$). The benefit in younger patients was observed in those with a negative PET2 result ($P=.034$), but was not

significant in patients with a positive PET2 result ($P=.117$). However, for both the overall PET2-positive population and PET2-positive patients younger than 60 years, there were few PFS events, reducing the power to detect a significant difference in the rates of PFS.

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Highlights in Lymphoma From the 60th American Society of Hematology Annual Meeting: Commentary

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Presentations given at the 60th American Society of Hematology (ASH) Annual Meeting provided important insights into the management of patients with lymphoma. A number of studies focused on brentuximab vedotin, in the frontline setting and in relapsed/refractory patients with Hodgkin lymphoma and peripheral T-cell lymphoma (PTCL). Data were also presented for the real-world use of chimeric antigen receptor (CAR) modified T-cell therapy, rituximab/bendamustine and rituximab/cytarabine before transplant in mantle cell lymphoma, and continued attempts to enhance and refine frontline diffuse large B-cell lymphoma (DLBCL) therapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).

Brentuximab Vedotin

Dr Steven Horwitz presented results of the ECH-ELON-2 trial (A Comparison of Brentuximab Vedotin and CHP With Standard-of-Care CHOP in the Treatment of Patients With CD30-Positive Mature T-Cell Lymphomas).¹ This randomized phase 3 study compared brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisone (CHP) vs CHOP for the frontline treatment of patients with CD30-positive PTCL. Brentuximab vedotin is an antibody-drug conjugate that targets CD30. It consists of an antibody linked to chemotherapy; the antibody locates the tumor cells and delivers the chemotherapy. ECH-ELON-2 is an important study for patients with PTCL, who have a suboptimal prognosis with standard chemotherapy. The standard treatment

for these patients is chemotherapy followed by autologous stem cell transplant administered as consolidation treatment during remission.

In the ECH-ELON-2 trial, treatment with brentuximab vedotin led to longer progression-free survival (PFS) and overall survival, as well as higher response rates.¹ The 3-year PFS was 57% with brentuximab vedotin plus CHP vs 44% with CHOP. The brentuximab vedotin arm had a 29% reduction in the risk of a progression event. The results of this study led to the approval of brentuximab vedotin as a frontline treatment for patients with CD30-positive T-cell lymphoma. This study is truly practice-changing, showing meaningful improvement in PFS and overall survival. Rates of toxicity were relatively similar between

the treatment arms. The rates of peripheral neuropathy were higher in the brentuximab vedotin arm, but the importance of the increased efficacy observed in a disease typically associated with dismal outcomes outweighs this increased toxicity.

A study from Dr Alison Moskowitz and colleagues evaluated nivolumab combined with brentuximab vedotin for patients with primary mediastinal large-cell lymphoma.² The standard regimen for patients with primary mediastinal large-cell lymphoma tends to be rituximab plus etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH). The majority of patients are cured with this regimen, but approximately 20% are not. The patients who are not cured with R-EPOCH tend to have very poor responses to subsequent therapies. The trial by Dr Moskowitz combined brentuximab vedotin with nivolumab, which has demonstrated efficacy in Hodgkin lymphoma.³ The results in primary mediastinal large-cell lymphoma were excellent. The overall response rate was 70%, and the complete response rate was 27%. Among the 30 patients, most had received 2 or more prior lines of therapy, and more than a third had received 3 or more lines. The results suggested that nivolumab plus brentuximab vedotin is a promising regimen for these patients. The addition of brentuximab vedotin to programmed death 1 (PD-1) blockade was associated with higher rates of overall response and complete response than monotherapy with the PD-1 antibody pembrolizumab in this setting.⁴

Further study is merited to confirm the value of this regimen in patients with relapsed/refractory primary mediastinal large-cell lymphoma. Currently, CAR T cells are approved for patients with relapsed/refractory primary mediastinal large B-cell lymphoma. Nivolumab plus brentuximab vedotin may provide an effective treatment option for these patients, either before or after CAR T-cell therapy. These promising data support the future investigation of

nivolumab plus brentuximab vedotin earlier in a patient's treatment course, perhaps as second-line therapy as a bridge to transplant or possibly even as part of frontline therapy.

Dr Robert Chen presented a phase 1 study of brentuximab vedotin plus the MDR1-inhibiting drug cyclosporine in patients with relapsed/refractory Hodgkin lymphoma.⁵ Brentuximab vedotin is very effective for Hodgkin lymphoma.⁶ Traditionally, this therapy has been used for patients with relapsed/refractory disease. It has been moved forward to the frontline space in patients with advanced-stage Hodgkin lymphoma.⁷ In general, clinicians are comfortable re-treating patients who have responded to prior brentuximab vedotin and have discontinued therapy and then subsequently relapsed. There is a proportion of patients who will respond again to brentuximab vedotin re-treatment. With use as part of frontline therapy, however, a strategy for dealing with brentuximab vedotin resistance is an unmet need. This trial builds on work performed in the laboratory at City of Hope demonstrating that the use of cyclosporine, which competitively inhibits the drug efflux pump MDR1, could reinduce sensitivity to brentuximab vedotin. Part of the process by which a Hodgkin lymphoma cell becomes resistant to brentuximab vedotin is that a drug efflux pump removes the cytotoxic agent delivered by the drug. By giving cyclosporine, it is possible to occupy the space that normally the cell would use to expel the cytotoxic agent delivered by brentuximab vedotin. Instead, the cytotoxic agent is trapped inside the cell because the drug efflux pumps will not remove it, thereby reinducing sensitivity to the drug.

The response rates with this regimen were excellent. The overall response rate was 67%, and the complete response rate was 33%.⁵ Several patients were able to undergo stem cell transplant after treatment with this regimen. The potential to reinduce

sensitivity to a drug is a powerful concept. We are now conducting a larger study to confirm these results.⁸ However, this study provides proof of concept that it is possible to replicate laboratory results and reinduce sensitivity to brentuximab vedotin.

Dr Catherine Diefenbach presented results from a phase 1 study of ipilimumab, nivolumab, and brentuximab vedotin in patients with relapsed/refractory Hodgkin lymphoma.⁹ In 2015, Dr Diefenbach presented a phase 1 study of brentuximab vedotin plus ipilimumab, which showed that rates of overall and complete responses were higher than what would be expected with brentuximab vedotin alone.¹⁰ The next regimen that was studied as part of this protocol was brentuximab vedotin plus nivolumab.¹¹ This combination was well-tolerated and effective, producing high rates of overall and complete responses.

The current study builds on the previous ones, asking whether the triplet combination of brentuximab, nivolumab, and ipilimumab would be tolerable and effective. The preliminary data presented by Dr Diefenbach showed a very high overall response rate of 95% and a complete response rate of 84% in evaluable patients.⁹ There were no unexpected toxicities beyond what was seen with the doublets. Rates of PFS were similar in patients who were pre- or post-transplant, but the numbers of these patients were small. In a previous study, the addition of ipilimumab to nivolumab did not improve efficacy, but it did increase toxicity.¹² In the study by Dr Diefenbach, ipilimumab was administered less frequently (at 1 mg/kg on day 1 every 12 weeks), a strategy that could potentially minimize toxicities and augment the immune effects. An ongoing study will randomly assign patients to treatment with the doublet regimen of brentuximab vedotin and nivolumab or the triplet regimen of brentuximab vedotin, nivolumab, and ipilimumab.¹³

In a study by Dr Joseph Connors, the addition of brentuximab vedotin to

doxorubicin, vinblastine, and dacarbazine (AVD) increased PFS as compared with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD).¹⁴ The rate of 2-year modified PFS per independent review was 81.0% with brentuximab vedotin plus AVD vs 74.4% with ABVD. The ECHELON-1 study (A Frontline Therapy Trial in Participants With Advanced Classical Hodgkin Lymphoma) used the new endpoint of modified PFS, which consisted of disease progression, death, and a modified event (defined as evidence of noncomplete response [positron emission tomography scan Deauville score 3-5] after completion of frontline therapy, followed by subsequent anticancer therapy [chemotherapy or radiotherapy]). The rate of 2-year standard PFS according to investigator assessment was 84.0% with brentuximab vedotin plus AVD vs 77.3% with ABVD. This study showed that brentuximab vedotin improved outcome as measured by modified PFS, as well as the standard PFS.

CAR T-Cell Therapy

Dr Loretta Nastoupil presented results from a real-world experience of axicabtagene ciloleucel, the C19-specific CAR T-cell therapy.¹⁵ This presentation and the abstract by Dr Caron Jacobson presented in the same session were 2 of the key lymphoma studies presented at the ASH meeting.¹⁶ Both studies confirmed the effectiveness of axicabtagene ciloleucel in a real-world population of patients treated at academic centers outside of a clinical trial. This real-world analysis included patients who did not meet the enrollment criteria of the original clinical trial, ZUMA-1 (Safety and Efficacy of KTE-C19 in Adults With Refractory Aggressive Non-Hodgkin Lymphoma).¹⁷ The analysis examined whether CAR T-cell therapy would be effective in this broader population, which may have included patients who were sicker or had more risk factors. The rates of best overall response at day

90 were 81% in the real-world analysis vs 82% in ZUMA-1. The rates of best complete response at day 90 were 57% vs 58%, respectively. Long-term results are not yet available, but at a median follow-up of approximately 4 months, the median PFS was 6.18 months, and the 6-month estimate of overall survival was 72%. Remission rates were similar to those seen in the clinical trial. The toxicities were also similar in the real-world study and ZUMA-1. This study, as well as the one by Dr Jacobson,¹⁶ confirmed that CAR T-cell therapy is effective, regardless of whether patients would have met the criteria for enrollment in the clinical trial.

Rituximab/Bendamustine and Rituximab/Cytarabine

A study presented by Dr Reid Merriam and colleagues evaluated frontline treatment with rituximab/bendamustine and rituximab/cytarabine in patients with mantle cell lymphoma who were eligible for transplant.¹⁸ This important study confirmed results that were seen in a much smaller study, which enrolled 23 patients, that was reported in 2016.¹⁹ These confirmatory findings from a larger study of 86 patients demonstrated that this strategy is indeed an effective induction regimen when given prior to autologous stem cell transplant that yields favorable outcomes. The rates of PFS were 85% at 3 years and 80% at 5 years, which compares favorably with other regimens used for transplant-eligible patients, such as the Nordic regimen.²⁰ This strategy condenses the treatment down to key drugs with potent anti-tumor activity: the monoclonal antibody rituximab plus bendamustine and cytarabine, which are among the most effective chemotherapies for mantle cell lymphoma. This regimen is being considered as a backbone in larger studies currently in development that are evaluating the addition of novel agents to frontline therapy.²¹

CHOP-Based Strategies

A study by Dr Franck Morschhauser and colleagues added venetoclax to rituximab plus CHOP (R-CHOP).²² Many studies have been conducted with the intention of improving R-CHOP; nevertheless, R-CHOP remains the standard frontline regimen for patients with DLBCL. This study showed that it may be possible to improve PFS by adding venetoclax to R-CHOP in patients who were BCL-2–positive. Patients with double-expressor or double-hit lymphoma have BCL-2 that is overexpressed or BCL-2 that is rearranged according to fluorescence in situ hybridization (FISH). The patients in both of these groups have a worse prognosis than typical DLBCL patients. Therefore, it was particularly promising to see that in patients who were BCL-2–positive, the addition of venetoclax to R-CHOP seemed to produce favorable outcomes. The benefit of adding venetoclax to R-CHOP or frontline anthracycline-containing chemotherapies is currently being explored as part of larger studies by cooperative groups. The study by Dr Morschhauser provides proof of concept that the addition of venetoclax to R-CHOP is reasonably safe. The addition of venetoclax did not appear to significantly impact the dose intensity of R-CHOP.

A study by Dr Viola Poeschel evaluated 4 cycles of CHOP plus rituximab (R-CHOP) followed by 2 cycles of single-agent rituximab vs 6 cycles of R-CHOP in young patients with favorable-prognosis DLBCL.²³ For many years, R-CHOP has been the standard treatment for DLBCL. There have been many efforts to improve on this regimen and increase the cure rate in treatment-naïve patients with DLBCL, particularly those at high risk. Investigators are trying to identify which types of patients are not responding to R-CHOP in order to improve outcomes. Attempts have been made by adding new drugs and extra chemotherapies, intensifying the regimen, and even performing

transplant after R-CHOP. None of these approaches have been effective across the board. The study by Dr Poeschel took the opposite approach, exploring whether there were patients in whom treatment could be safely de-escalated. This study enrolled a patient population with a very favorable risk profile. The patients had an age-adjusted International Prognostic Index score of 0, no bulky disease, and a low tumor burden. Patients were randomly assigned to treatment with 4 or 6 cycles of R-CHOP. The study, which was designed as a noninferiority trial, showed that PFS, overall survival, and response rates were similar regardless of whether the patients received 4 or 6 cycles of therapy. At 36 months, PFS was 94% with 6 cycles vs 96% with 4 cycles. This study is important, as we are always hoping to spare our patients toxicity.

Dr Anas Younes presented results of a trial evaluating ibrutinib plus the standard up-front chemotherapy, R-CHOP.²⁴ Among patients with DLBCL, ibrutinib works primarily in the non-germinal center subtype. The study enrolled patients of all ages with non-germinal center subtype DLBCL. The study found that ibrutinib added to R-CHOP was not superior to R-CHOP alone. The rates of overall response were 89.3% with ibrutinib vs 93.1% without ibrutinib. However, in the younger population of patients (<60 years), the addition of ibrutinib did improve outcomes. Older patients (≥60 years) had higher rates of serious adverse events and adverse events leading to treatment discontinuation. The study results suggested that ibrutinib might be an important therapy for younger patients with non-germinal center subtype DLBCL. A confirmatory study is needed, however, since this trial was not powered to evaluate the primary outcome in this subgroup of patients.

Disclosure

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Co, Kite Pharma/Gilead, and Adaptive Biotechnologies. He has received research funding/grants from Genentech, Bristol-Myers Squibb, Immune Design, Astra-Zeneca, Merck & Co, Pharmacyclics, Seattle Genetics, Kite Pharma, and Gilead Sciences.

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