

A SPECIAL MEETING REVIEW EDITION

Highlights in Lymphoma From the 2019 American Society of Clinical Oncology Annual Meeting

A Review of Selected Presentations From the 2019 ASCO Annual Meeting

• May 31-June 4, 2019 • Chicago, Illinois

Special Reporting on:

- Brentuximab Vedotin With Chemotherapy for Stage 3/4 Classical Hodgkin Lymphoma: Three-Year Update of the ECHELON-1 Study
- Umbralisib Monotherapy Demonstrates Efficacy and Safety in Patients With Relapsed/Refractory Marginal Zone Lymphoma: A Multicenter, Open Label, Registration Directed Phase II Study
- Response to Brentuximab Vedotin by CD30 Expression: Results From Five Trials in PTCL, CTCL, and B-Cell Lymphomas
- Sintilimab for Relapsed/Refractory Extranodal NK/T-Cell Lymphoma: A Multicenter, Single-Arm, Phase 2 Trial (ORIENT-4)
- Response to A+CHP by CD30 Expression in the ECHELON-2 Trial
- Polatuzumab Vedotin + Obinutuzumab and Lenalidomide in Patients With Relapsed/Refractory Follicular Lymphoma: Interim Analysis of a Phase Ib/II Trial
- First-Line Therapy of T-Cell Lymphoma: Allogeneic or Autologous Transplantation for Consolidation—Final Results of the AATT Study
- Lisocabtagene Maraleucel (Liso-Cel) Treatment of Patients With Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma and Secondary CNS Lymphoma: Initial Results From TRANSCEND NHL 001
- Rituximab Maintenance for Patients With Diffuse Large B-Cell Lymphoma in First Complete Remission: Results From a Randomized HOVON-Nordic Lymphoma Group Phase III 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^{1,2}

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

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

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

5.8 Hepatotoxicity

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

5.9 Progressive Multifocal Leukoencephalopathy

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

5.10 Pulmonary Toxicity

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

5.11 Serious Dermatologic Reactions

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

5.12 Gastrointestinal Complications

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

5.13 Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, ADCETRIS can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of ADCETRIS in pregnant women. In animal reproduction studies, brentuximab vedotin caused embryo-fetal toxicities, including significantly decreased embryo viability and fetal malformations at maternal exposures that were similar to the clinical dose of 1.8 mg/kg every three weeks.

Advise females of reproductive potential to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS. Advise a pregnant woman of the potential risk to the fetus.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reactions (≥20%) in combination with 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, CD3-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 ≥2% more in recipients of ADCETRIS + CHP were nausea, diarrhea, fatigue or asthenia, mucositis, pyrexia, vomiting, and anemia. Other common (≥10%) adverse reactions observed ≥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 ≥ 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 (≥99%), post-implantation loss (≥99%), decreased numbers of live fetuses, and external malformations (i.e., umbilical hernias and malrotated hindlimbs). Systemic exposure in animals at the brentuximab vedotin dose of 3 mg/kg is approximately the same exposure in patients with cHL or sALCL who received the recommended dose of 1.8 mg/kg every three weeks.

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating ADCETRIS therapy.

Contraception

Females

Advise females of reproductive potential to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS. Advise females to immediately report pregnancy.

Males

ADCETRIS may damage spermatozoa and testicular tissue, resulting in possible genetic abnormalities. Males with female sexual partners of reproductive potential should use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Infertility

Males

Based on findings in rats, male fertility may be compromised by treatment with ADCETRIS.

8.4 Pediatric Use

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

8.5 Geriatric Use

In the clinical trial of ADCETRIS in combination with 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 ≥Grade 3 and 49% had serious adverse reactions. Among patients younger than age 65, 62% had adverse reactions ≥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 adcetriscpro.com



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

A 3-year follow-up of the ECHELON-1 trial (A Frontline Therapy Trial in Participants With Advanced Classical Hodgkin Lymphoma) demonstrated sustained efficacy with brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (AVD) as treatment for stage 3/4 classical Hodgkin lymphoma.¹ The trial compared brentuximab vedotin plus AVD vs doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) among patients from 21 countries. The patients were randomly assigned to receive 6 cycles of brentuximab vedotin plus AVD (n=664) or ABVD (n=670) intravenously on days 1 and 15 of each cycle. Patients were assessed

by computed tomography (CT)/PET scans before and after treatment. PET status at the end of cycle 2 (PET2) was considered negative among patients with a Deauville score of 1, 2, or 3 and positive among those with a score of 4 or 5.

Initial results from the phase 3 ECHELON-1 trial showed that brentuximab vedotin plus AVD improved outcomes, with a hazard ratio (HR) for modified progression-free survival (PFS) of 0.77 (95% CI, 0.60-0.98).² The 3-year follow-up study evaluated both investigator-assessed PFS among the intention-to-treat (ITT) population as well as safety, with particular attention to peripheral neuropathy.¹ At

a median follow-up of 37.1 months, the PFS rate was 83.1% with brentuximab vedotin plus AVD vs 76.0% with ABVD. Treatment with brentuximab vedotin plus AVD reduced the risk of progression or death at 3 years by 30% compared with ABVD (HR, 0.704; 95% CI, 0.550-0.901; $P=.005$; Figure 1). Subgroup analyses based on age, International Prognostic Score, PET2 status, and stage of disease also reflected superior PFS with brentuximab vedotin plus AVD compared with ABVD.

In the initial trial results, peripheral neuropathy was reported among 67% of patients receiving brentuximab vedotin plus AVD and 43% of those

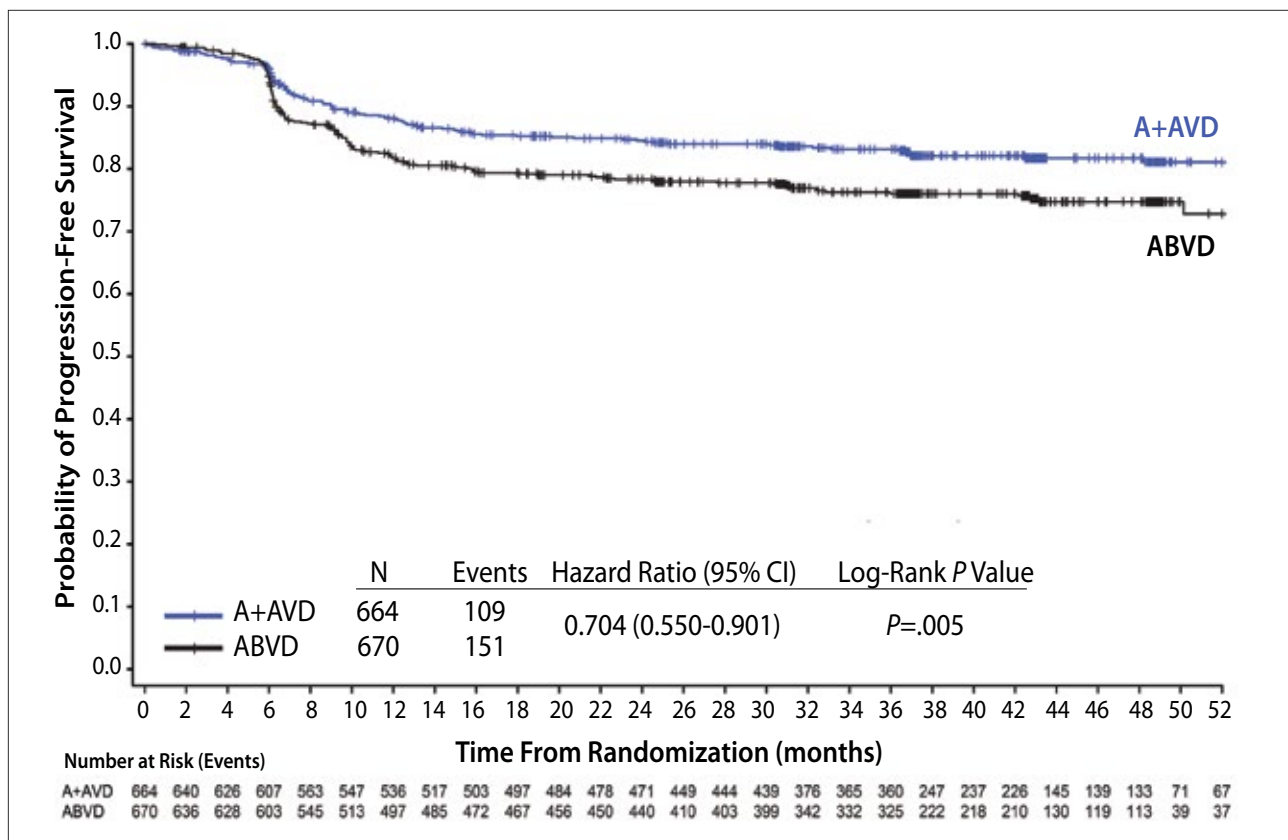


Figure 1. Probability of progression-free survival among patients in a 3-year follow-up analysis of the phase 3 ECHELON-1 trial. A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ECHELON-1, A Frontline Therapy Trial in Participants With Advanced Classical Hodgkin Lymphoma. Adapted from Straus DJ et al. ASCO abstract 7532. *J Clin Oncol.* 2019;37(suppl 15).¹

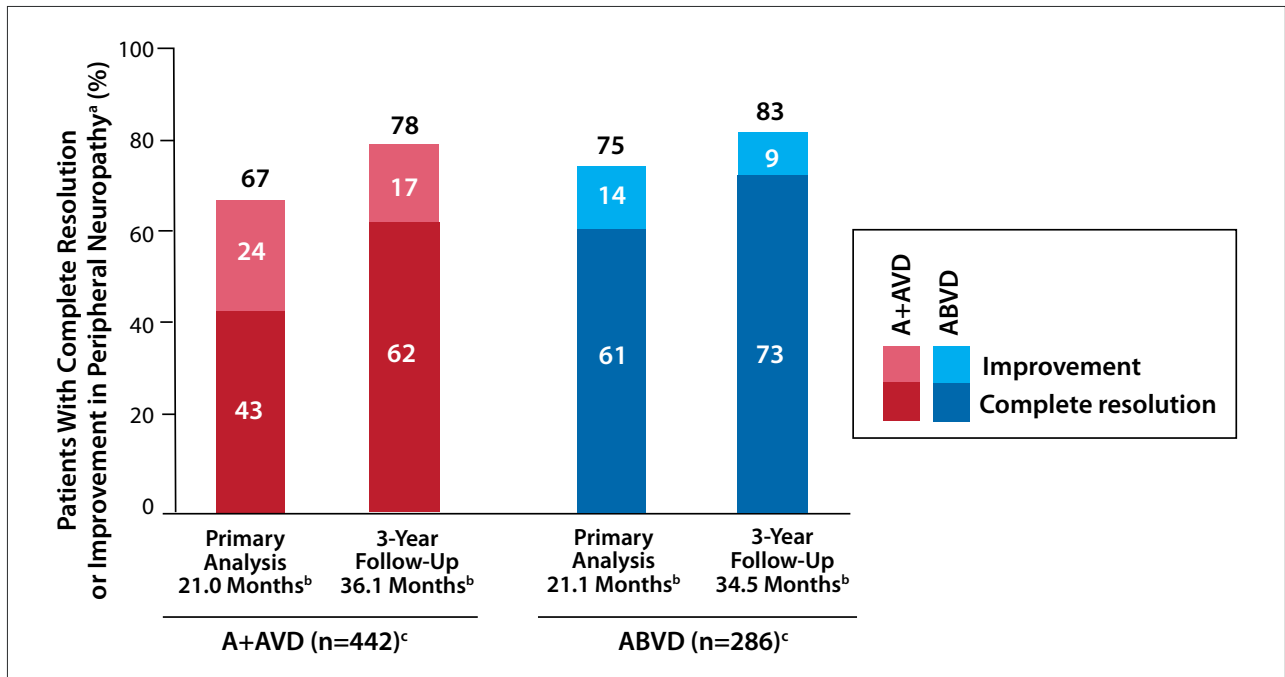


Figure 2. Improvement in peripheral neuropathy in a 3-year follow-up analysis of the phase 3 ECHELON-1 trial. ^aResolution was defined as event outcome of “resolved” or “resolved with sequelae.” Improvement was defined as “improved by ≥ 1 grade from worst grade as of the latest assessment.” ^bMedian follow-up from end of treatment for the cohort with unresolved peripheral neuropathy. ^cTotal patients with peripheral neuropathy at end of treatment. A+AVD, brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ECHELON-1, A Frontline Therapy Trial in Participants With Advanced Classical Hodgkin Lymphoma. Adapted from Straus DJ et al. ASCO abstract 7532. *J Clin Oncol.* 2019;37(suppl 15).¹

receiving ABVD (Figure 2).² By the 3-year analysis, these cases improved completely or partially in 78% vs 83%, respectively. Among the patients with complete resolution of peripheral neuropathy, the median time to resolution was 28 weeks after the end of treatment with brentuximab vedotin plus AVD and 14 weeks after ABVD. For those patients with partial improvement, the median time to improvement was 40 weeks vs 32 weeks, respectively.

The study showed that initial treatment of advanced classical Hodgkin lymphoma with 6 cycles of brentuximab vedotin plus AVD provided strong, sustained benefits in all subgroups. Notably, brentuximab vedotin plus AVD improved PFS for both PET2-positive and PET2-negative patients. The study authors concluded that the 30% reduction in disease progression or death at 3 years, along with improvement in peripheral neuropathy over time, sug-

gests that brentuximab vedotin plus AVD has a more favorable benefit/risk profile compared with ABVD.

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Umbralisib Monotherapy Demonstrates Efficacy and Safety in Patients With Relapsed/Refractory Marginal Zone Lymphoma: A Multicenter, Open Label, Registration Directed Phase II Study

Umbralisib has shown evidence of activity in patients with relapsed or refractory hematologic malignancies. This next-generation phosphoinositide 3-kinase delta (PI3K δ) inhibitor may have improved selectivity and a distinct safety profile

compared with earlier agents.^{1,2} A phase 1 trial showed a lower rate of colitis.²

The multicenter, multicohort phase 2b UNITY-NHL trial (Study to Assess the Efficacy and Safety of Ublituximab + TGR-1202

With or Without Bendamustine and TGR-1202 Alone in Patients With Previously Treated Non-Hodgkins Lymphoma) investigated the efficacy and safety of umbralisib alone and in various combinations in patients with relapsed or refractory non-Hodgkin

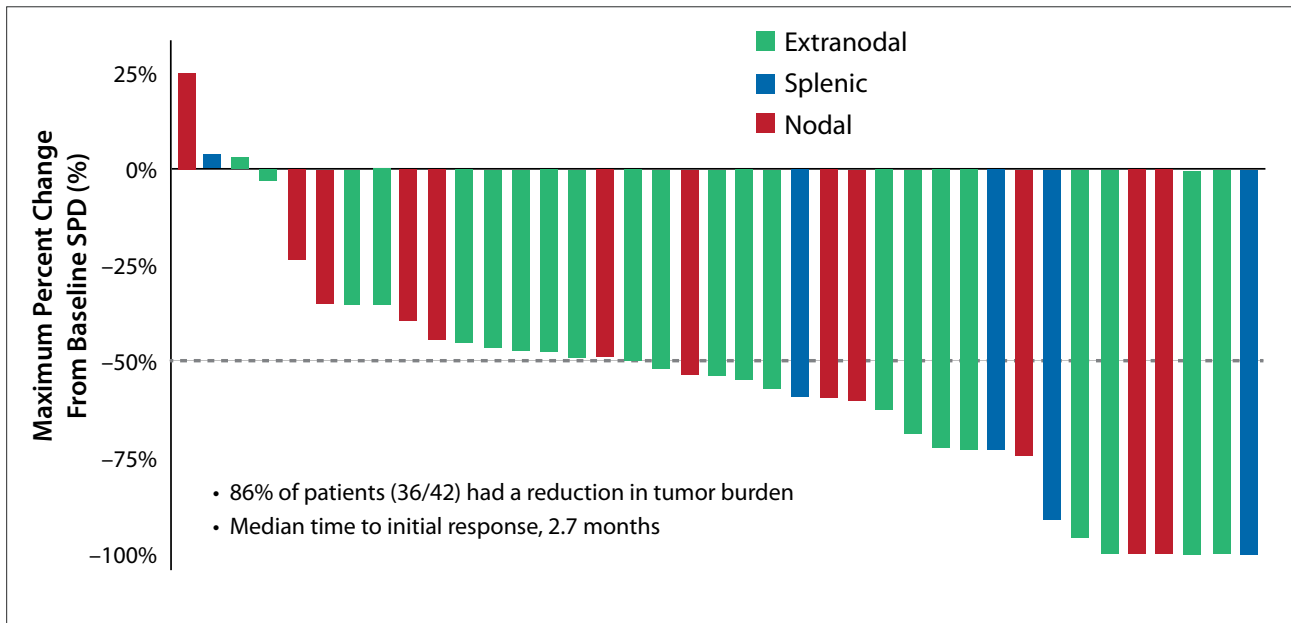


Figure 3. Best percent change in tumor lesions among patients treated with umbralisib in the phase 2b UNITY-NHL trial. SPD, sum of the products of diameters; UNITY-NHL, Study to Assess the Efficacy and Safety of Ublituximab + TGR-1202 With or Without Bendamustine and TGR-1202 Alone in Patients With Previously Treated Non-Hodgkins Lymphoma. Adapted from Fowler NH et al. ASCO abstract 7506. *J Clin Oncol.* 2019;37(suppl 15).¹

lymphoma. Dr Felipe Samaniego presented results for patients with marginal zone lymphoma, who received single-agent umbralisib at an oral daily dose of 800 mg until progressive disease or unacceptable toxicity.¹ The primary endpoint of the study was the overall response rate (ORR). The secondary endpoints were duration of response, PFS, time to response, and safety.

The trial enrolled 72 patients with marginal zone lymphoma. The interim efficacy analysis included 42 patients who received 9 or more treatment cycles, with a median duration of 10.1 months (range, 0.7-15.7). Their median age was 67 years (range, 34-81). Among these patients, 45% had received 1 prior line of therapy, and 55% had received 2 or more prior lines of therapy.

The median follow-up duration was 12.5 months (range, 8.3-18.5 months), with 55% of patients still receiving treatment at the time of the report. The cause of treatment discontinuation included progressive disease in 10 patients and treatment-related

ABSTRACT SUMMARY Smart Start: Final Results of Rituximab, Lenalidomide, and Ibrutinib Lead-In Prior to Combination With Chemotherapy for Patients With Newly Diagnosed Diffuse Large B-Cell Lymphoma

The phase 2 Smart Start trial evaluated rituximab, lenalidomide, and ibrutinib in patients with newly diagnosed DLBCL (Abstract 7508). The 49 evaluable patients had newly diagnosed non-germinal center B-cell DLBCL and received rituximab, lenalidomide, and ibrutinib for 2 cycles before the addition of chemotherapy. Prior to chemotherapy, the ORR was 86%, with a CR in 36%. Disease burden decreased substantially with the combination prior to chemotherapy. After chemotherapy was added, the ORR reached 98% in the ITT population. Approximately 50% of patients developed nausea. Peripheral sensory neuropathy and diarrhea each occurred in almost half of patients. Two fatalities were reported.

adverse events (AEs) in 5 patients.

The ORR was 52% with umbralisib, according to investigator assessment and independent review. The clinical benefit rate—a composite of partial response (PR), complete response (CR), and stable disease—was 88%.

According to independent review, umbralisib had activity across subtypes.

The ORR was 57% in patients with extranodal marginal zone lymphoma, 42% in those with nodal marginal zone lymphoma, and 43% in those with splenic marginal zone lymphoma. ORR was 53% among patients who had received prior chemoimmunotherapy, 38% among those who were refractory to their most recent line of therapy, and 44% in those who had

ABSTRACT SUMMARY Feasibility of Brentuximab Vedotin as Consolidation Therapy After Autologous Stem Cell Transplantation in Children and Adolescents (<18 Years) With Early-Relapse Hodgkin Lymphoma

A retrospective review examined the feasibility of consolidation therapy with brentuximab vedotin following autologous SCT in pediatric patients with Hodgkin lymphoma and early relapse (Abstract e19012). The 6 patients in the study were ages 12 to 18 years. Five of the patients had high-risk disease. Patients were stratified according to risk, and treatment was adjusted based on individual responses. Brentuximab vedotin consolidation therapy was given every 3 weeks for a maximum of 16 cycles. The duration of PFS ranged from 12 to 30 months. Grade 3 AEs included 2 cases of neutropenia, as well as 2 cases of neuropathy that led to treatment discontinuation.

relapsed after 2 or more prior lines of therapy.

The median duration to initial response with umbralisib was 2.7 months. A reduction in tumor burden occurred in 86% of patients (Figure 3). The median duration of response with umbralisib was not reached among 22 evaluable patients. The median PFS was also not reached among 42 evalu-

able patients. The estimated rate of 12-month PFS was 66%.

AEs were evaluated in 69 patients, who had received umbralisib for a median of 6.9 months. Umbralisib was generally well tolerated. No deaths or cases of colitis were reported. Dose reductions owing to AEs were required by 9% of patients, and another 14% of patients discontinued umbralisib

because of AEs that were possibly related to treatment. Diarrhea was the most common AE, ranging from grades 1 to 3. The prevalence of grade 3 diarrhea was 10%. Grade 3 elevations of the liver enzymes aspartate aminotransferase and alanine aminotransferase (ALT) each occurred in 9% of patients. Increases in liver enzymes mostly diminished throughout the course of the study, with only 1 patient showing an elevated ALT after 6 cycles. After 6 months, no patients discontinued umbralisib owing to a treatment-related AE.

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Response to Brentuximab Vedotin by CD30 Expression: Results From Five Trials in PTCL, CTCL, and B-Cell Lymphomas

Treatment with brentuximab vedotin has been studied in several types of lymphoma.¹ A component of brentuximab vedotin, the antimetabolic drug monomethyl auristatin E (MMAE), acts upon cells expressing the CD30 cell surface antigen.² However, there are additional possible explanations for the activity of brentuximab vedotin against tumor cells.¹ These may include macrophage-mediated cellular phagocytosis, cellular immune response, and a bystander-killing effect.³⁻⁵ Additionally, responses to brentuximab vedotin have not consistently reflected levels of CD30 expression.⁶⁻¹⁰ A study examined the results of 5 prospective clinical trials to identify any association between CD30

expression and the efficacy of brentuximab vedotin.¹ This study analyzed the results of 5 prospective clinical trials evaluating brentuximab vedotin for relapsed/refractory lymphoma. The analysis included 275 patients who received brentuximab vedotin monotherapy for the treatment of relapsed/refractory peripheral T-cell lymphoma (PTCL), cutaneous T-cell lymphoma (CTCL), or B-cell non-Hodgkin lymphoma (NHL). The 5 trials were the phase 2 SGN35-012 trial (parts A and C), the phase 2 35-IST-030 trial, the phase 3 ALCANZA trial (Brentuximab Vedotin or Physician's Choice in CD30-Positive Cutaneous T-Cell Lymphoma), the phase 2 35-IST-001 trial, and the phase 2 35-IST-002 trial.

CD30 expression was quantified through immunohistochemistry. Patients were grouped by CD30 expression levels of greater than or equal to 10%, less than 10%, and undetectable. These levels were compared with data for the ORR and duration of response. For some patients in the ALCANZA and 35-IST-002 trials, more than 1 measurement of CD30 expression was available. When CD30 expression was calculated using averaged values in the ALCANZA and 35-IST-002 studies, expression was less than 10% in 140 patients, including 60 patients with undetectable expression. When the analysis included the lowest measured CD30 values from these studies, the number of patients with less than 10%

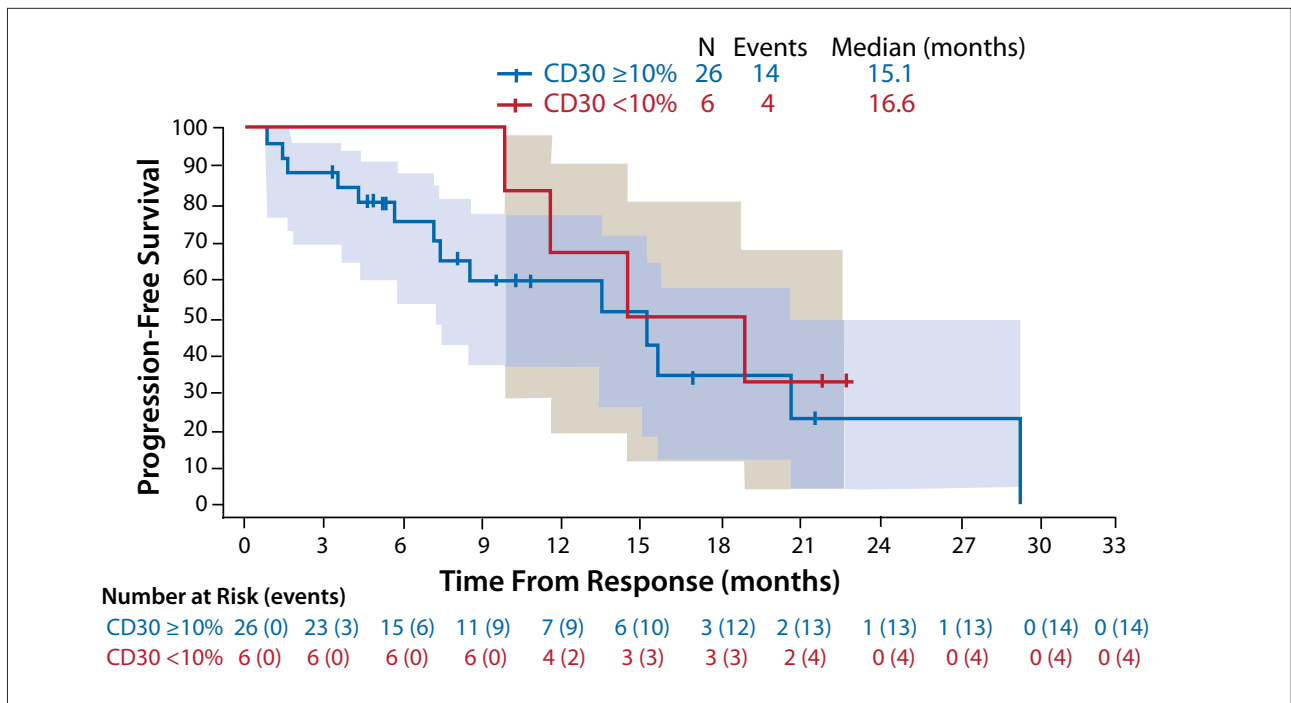


Figure 4. Progression-free survival according to the level of CD30 expression in an analysis of patients with CTCL treated with brentuximab vedotin in the ALCANZA trial. ALCANZA, Brentuximab Vedotin or Physician's Choice in CD30-Positive Cutaneous T-Cell Lymphoma; CTCL, cutaneous T-cell lymphoma. Adapted from Jagadeesh D et al. ASCO abstract 7543. *J Clin Oncol.* 2019;37(suppl 15).¹

expression was 153, of whom 80 had undetectable expression.

The analysis found that ORR values did not consistently correspond to CD expression.¹ Only one comparison, among patients with CTCL in the ALCANZA trial, suggested a possible trend between higher ORR and high CD30 expression. However, the 95% CIs for ORR overlapped with each other across all categories. Among patients with B-cell NHL in the SGN35-012 study, no discernible trend appeared between the level of CD30 expression and ORR.

The level of CD30 expression did not correspond to the median duration of response across the studies. For patients with CTCL in the ALCANZA trial, based on averaged CD30 expression levels, the median duration of response was 15.1 months among those with 10% or higher CD30 expression and 16.6 months among those with a level below 10% ($P=.46$; Figure 4). Among patients with B-cell NHL in the SGN35-012

ABSTRACT SUMMARY MAGNIFY: Phase IIIb Interim Analysis of Induction R² Followed by Maintenance in Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

A phase 3b trial evaluated lenalidomide plus rituximab with extended rituximab maintenance in patients with relapsed or refractory follicular lymphoma or marginal zone lymphoma (Abstract 7513). The ORR was 73% among 310 patients evaluable for efficacy. Subgroup analyses showed ORRs of 74% in patients with follicular lymphoma, 65% in those with marginal zone lymphoma, 63% in those with rituximab-refractory disease, and 68% in those with early relapse. Patients refractory to both rituximab and an alkylating agent had an ORR of 51%. Overall, the median PFS was 36.0 months (95% CI, 26.5 to not reached). The median PFS was 30.2 months (95% CI, 23.0 to not reached) in patients with follicular lymphoma and 38.4 months (95% CI, 26.5-38.4) in those with marginal zone lymphoma. The most frequent treatment-emergent grade 3/4 AEs were neutropenia in 34%, thrombocytopenia in 6%, fatigue in 5%, and leukopenia in 5%.

study, the median duration of response was 3.9 months in those with 10% or higher CD30 expression, 8.3 months in those with expression below 10%, and 11.6 months in those with undetectable expression ($P=.78$).

The study investigators concluded that the response and duration of response seen with brentuximab vedotin did not appear to be associated with levels of CD30 expression. They suggested that further elucidation of

this drug's mechanisms of action may help to improve outcomes.

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Sintilimab for Relapsed/Refractory Extranodal NK/T-Cell Lymphoma: A Multicenter, Single-Arm, Phase 2 Trial (ORIENT-4)

The fully human antibody sintilimab targets programmed death 1 (PD-1) with high affinity and receptor occupancy.¹⁻³ The single-arm phase 2 ORIENT-4 trial (Efficacy and Safety Evaluation of IBI308 in Patients With Relapsed/Refractory Extranodal NK/T Cell Lymphoma, Nasal Type: A Multi-

center, Single Arm, Phase 2 Study) evaluated sintilimab in relapsed or refractory extranodal NK/T-cell lymphoma (ENKTL).¹ Sintilimab was administered at 200 mg every 3 weeks until disease progression, death, unacceptable toxicity, or withdrawal from the trial. At the time of data cutoff, 28 patients with relapsed or refractory

ENKTL received sintilimab, although the planned enrollment had allotted for 60 patients. Tumor response was evaluated with PET/CT and CT/magnetic resonance imaging (MRI) with contrast. After week 24, only CT/MRI with contrast was used.

The patients' median age was 39.8 years (range, 19-65 years). Most patients (60.7%) were male. The Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 10.7%, 1 in 85.7%, and 2 in 3.6%. The median time from initial diagnosis was 22.0 months. The median number of prior lines of chemotherapy was 3.0, and 78.6% of patients had received prior radiotherapy. Two patients (7.1%) had undergone prior autologous stem cell transplant (SCT). Disease was refractory to asparaginase-based therapy in 12 patients (42.9%). Sixteen patients had relapsed disease (57.1%).

Sintilimab showed clinical activity among patients with relapsed or refractory ENKTL. The ORR was 67.9% (95% CI, 47.6-84.1). Two patients (7.1%) had a CR, and 17 patients (60.7%) had a PR. The ORR included 4 patients who developed pseudoprogressive disease before their response. Stable disease occurred in 5 patients

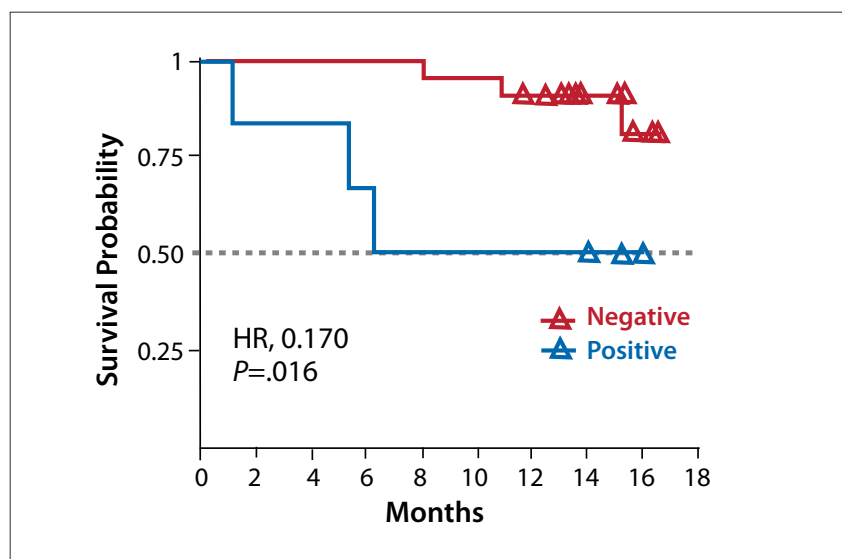


Figure 5. Overall survival according to bone marrow involvement among patients treated with sintilimab in the phase 2 ORIENT-4 trial. HR, hazard ratio; ORIENT-4, Efficacy and Safety Evaluation of IBI308 in Patients With Relapsed/Refractory Extranodal NK/T Cell Lymphoma, Nasal Type: A Multicenter, Single Arm, Phase 2 Study. Adapted from Tao R et al. ASCO abstract 7504. *J Clin Oncol*. 2019;37(suppl 15).¹

(17.9%), and disease progression was seen in 3 (10.7%). One patient was not evaluable. The disease control rate of 85.7% included 5 patients who experienced pseudoprogressive disease before developing stable disease or responding to treatment. The study authors noted that early disease progression did not correlate with poor outcome.

The median time to response was 1.3 months (range, 1.2-5.5), and the median duration of response was 4.1 months. A total of 19 patients were still receiving sintilimab at the time of the report. At a median follow-up of 15.4 months, the median overall survival (OS) was not reached. The 1-year rate of OS was 82.1%. A subgroup analysis showed that a superior ORR was associated with Epstein-Barr virus negativity, absence of B symptoms, normal lactate dehydrogenase, and negative bone marrow involvement (Figure 5). In a subgroup analysis, the absence of bone marrow involvement was associated with a higher OS (HR, 0.17; $P=.016$). No association with OS was seen with relapsed vs refractory disease (HR, 0.604; $P=.557$).

Most treatment-related AEs were grade 1 or 2. There were no grade 4 or 5 treatment-related AEs. The most common all-grade treatment-related AEs were decreased lymphocyte count (46.4%) and fever (42.9%). The patients' quality of life significantly improved from baseline (Figure 6).

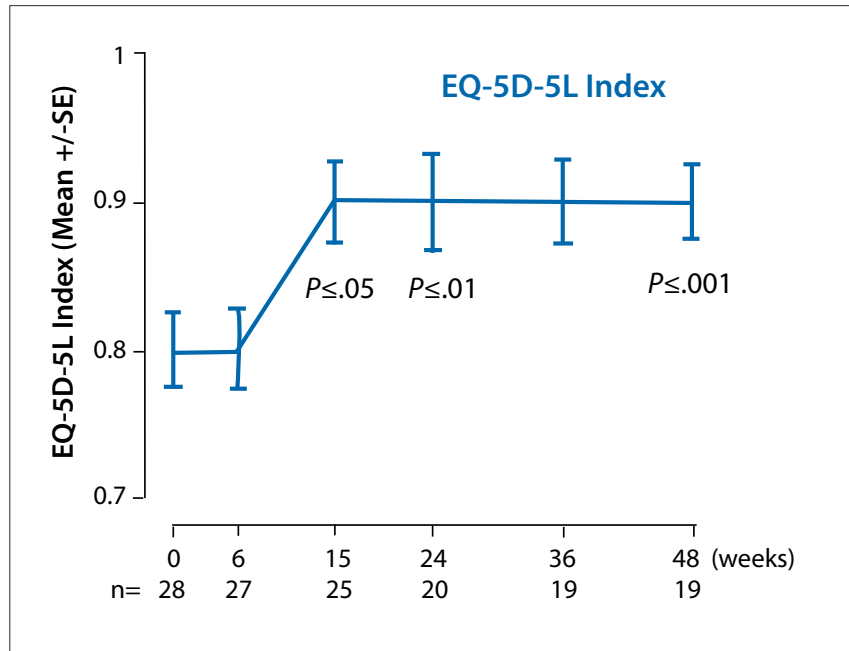


Figure 6. Quality of life according to the EQ-5D-5L Index among patients treated with sintilimab in the phase 2 ORIENT-4 trial. Quality of life was measured at baseline and at each subsequent evaluation of tumor response. EQ-5D-5L, European Quality of Life 5-Dimensions; ORIENT-4, Efficacy and Safety Evaluation of IBI308 in Patients With Relapsed/Refractory Extranodal NK/T Cell Lymphoma, Nasal Type: A Multicenter, Single Arm, Phase 2 Study; SE, standard error. Adapted from Tao R et al. ASCO abstract 7504. *J Clin Oncol.* 2019;37(suppl 15).¹

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Response to A+CHP by CD30 Expression in the ECHELON-2 Trial

The antibody-drug conjugate brentuximab vedotin selectively interacts with the CD30 cell surface antigen associated with some lymphoproliferative disorders.^{1,2} A component of brentuximab vedotin, MMAE, exhibits antimetabolic activity.³ However, brentuximab vedotin may also exert antitumor activity through additional mechanisms of action, and

the association between response and levels of CD30 expression is not confirmed.^{1,4-6}

In the phase 3 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), brentuximab vedotin plus cyclophosphamide, doxorubicin,

and prednisone (CHP) was superior to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in treatment-naïve patients with CD30-expressing PTCL.⁷ A follow-up analysis evaluated whether treatment response was related to CD30 expression among patients with angioimmunoblastic T-cell lymphoma (AITL; n=29) or PTCL not otherwise specified

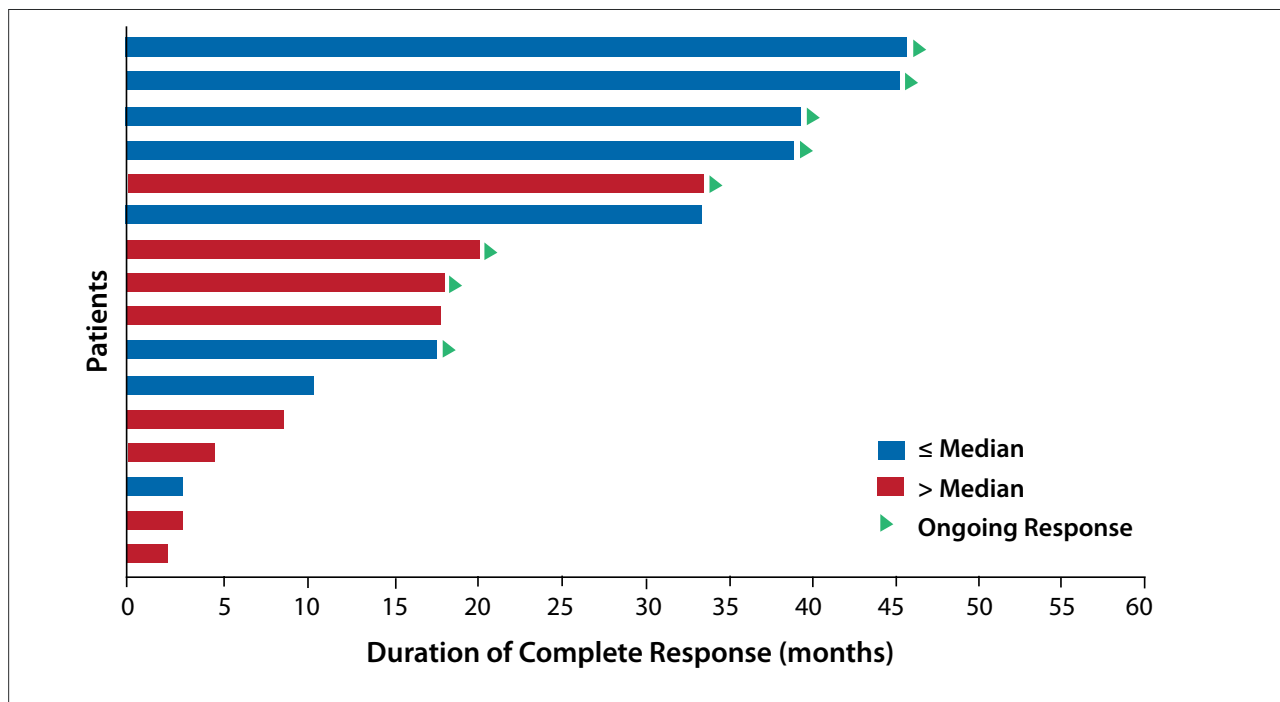


Figure 7. Duration of complete response according to the level of CD30 expression among patients with AITL receiving brentuximab vedotin plus CHP in the phase 3 ECHELON-2 trial. AITL, angioimmunoblastic T-cell lymphoma; CHP, cyclophosphamide, doxorubicin, and prednisone; ECHELON-2, A Comparison of Brentuximab Vedotin and CHP With Standard-of-Care CHOP in the Treatment of Patients With CD30-Positive Mature T-Cell Lymphomas. Adapted from Advani RH et al. ASCO abstract 7538. *J Clin Oncol.* 2019;37(suppl 15).¹

ABSTRACT SUMMARY Cost-Effectiveness of Brentuximab Vedotin With Chemotherapy in Frontline Treatment of CD30-Expressing Peripheral T-Cell Lymphoma

An analysis of the ECHELON-2 study evaluated the cost-effectiveness of CHOP and brentuximab vedotin plus CHP as initial treatment for CD30-expressing PTCL (Abstract e19060). Data from the ECHELON-2 study regarding PFS, postprogression survival, death, and European Quality of Life 5-Dimensions were analyzed in conjunction with medical resources and cost data derived from a search of the literature. Brentuximab vedotin plus CHP added 2.92 undiscounted years of PFS and 3.38 years of OS compared with CHOP in the predictive model. An estimated 1.79 quality-adjusted life years were added using brentuximab vedotin plus CHP, with an incremental cost-effectiveness ratio of \$98,987. This ratio ranged from \$64,000 to \$154,000, depending on model parameters. The authors estimated a probability of 75% that brentuximab vedotin plus CHP was more cost-effective than CHOP, using a willingness-to-pay threshold of \$150,000.

(PTCL-NOS; n=28) who had received brentuximab vedotin plus CHP.¹

The level of CD30 expression was measured with immunohistochemistry. Among the patients with AITL,

90% had a CD30 expression level of 10% to 30%, with a mean level of 20% and a median of 18%. The patients with PTCL-NOS had a wider range of CD30 expression. Their mean

CD30 expression level was 41%, and their median level was 25%.

Patient responses to brentuximab vedotin plus CHP were broadly distributed across the range of CD30 expression levels. Among patients with AITL who had achieved a CR, 8 had levels of CD30 expression above the median for AITL, and 8 had levels at or below the median ($P=.84$; Figure 7). Among the patients with lower expression, 5 had a CD30 expression level of 10%. Among patients with AITL who had a PR, 1 had a CD30 expression level above the median, and 3 had levels at or below the median.

Among patients with PTCL-NOS who achieved a CR, 8 had CD30 expression above the median for this subtype, and 10 had CD30 expression at or below the median ($P=.44$). Four patients had a CD30 expression level of 10%. PRs were reported in 2 patients with CD30 expression above the median, and in 2 patients below

the median (at 10% expression). The duration of CR appeared unrelated to CD30 expression levels for both AITL ($P=.30$) and PTCL-NOS ($P=.90$).

This analysis therefore suggested that levels of CD30 expression did not correspond to response to treatment with brentuximab vedotin plus CHP.¹ CRs were reported even in patients with a CD30 expression of 10%. The study authors recommended evaluation of CD30 expression below 10%, a level that was not assessed in this analysis.

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ABSTRACT SUMMARY Sintilimab for Relapsed/Refractory Classical Hodgkin Lymphoma: Extended Follow-Up on the Multicenter, Single-Arm Phase II ORIENT-1 Study

Sintilimab showed clinical activity in patients with relapsed/refractory classical Hodgkin lymphoma in the phase 2 ORIENT-1 study (Shi Y et al. *Lancet Haematol*. 2019;6[1]:e12-e19). The study authors presented extended follow-up results for 96 patients, 70 of whom were still receiving treatment at the time of the analysis (Abstract 7533). Sintilimab was given at 200 mg intravenously every 3 weeks for up to 24 months. The ORR was 85.4% (95% CI, 76.7%-91.8%), with 29.2% of patients showing a CR. The disease control rate was 97.9% (95% CI, 92.7%-99.7%), and 2.1% of patients developed progressive disease. The median PFS and median duration of response both had not been reached by the median follow-up of 14 months. Treatment-related grade 3/4 AEs occurred in 26.0% of patients. The authors noted that the safety profile was similar to those of other monoclonal antibody anti-PD-1 therapies in classical Hodgkin lymphoma.

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Polatuzumab Vedotin + Obinutuzumab and Lenalidomide in Patients With Relapsed/Refractory Follicular Lymphoma: Interim Analysis of a Phase Ib/II Trial

Polatuzumab vedotin is a first-in-class antibody-drug conjugate that targets CD79b, which is expressed in follicular lymphoma and diffuse large B-cell lymphoma (DLBCL).¹ After polatuzumab vedotin binds to CD79b on tumor cells, it is internalized. It then disrupts cellular division, triggering apoptosis. Dr Catherine Diefenbach and colleagues presented an interim analysis of an open-label, single-arm phase 1b/2 trial of polatuzumab vedotin plus obinutuzumab and lenalidomide in patients with relapsed or refractory follicular lymphoma. The patients were initially enrolled in a dose-escalation cohort.² They received

escalating doses of polatuzumab vedotin at 1.4 mg/kg or 1.8 mg/kg and lenalidomide at 10 mg, 15 mg, or 20 mg. Obinutuzumab was administered at a standard fixed dose of 1000 mg. The recommended phase 2 doses were 20 mg of lenalidomide and 1.4 mg/kg of polatuzumab vedotin.

In both phases, all patients initially received induction treatment consisting of 6 cycles of polatuzumab vedotin, obinutuzumab, and lenalidomide. The primary efficacy endpoint was CR at the end of induction, as assessed by independent review. Patients with a CR, PR, or stable disease could receive maintenance treatment with lenalidomide (admin-

istered on a 28-day cycle for up to 1 year) and obinutuzumab (administered every 2 months for up to 24 months).

The trial enrolled patients ages 18 years or older with relapsed or refractory follicular lymphoma of grades 1 to 3a. Patients had histologically confirmed CD20-positive tumors and 1 or more bidimensionally measurable lesions reaching at least 1.5 cm in 1 direction. They had an ECOG performance status of 0 to 2. Exclusion criteria were 3b disease; previous allogeneic SCT transplant; relapse within 100 days of autologous SCT; peripheral neuropathy of grade 2 or higher; resistance to lenalidomide; insufficient

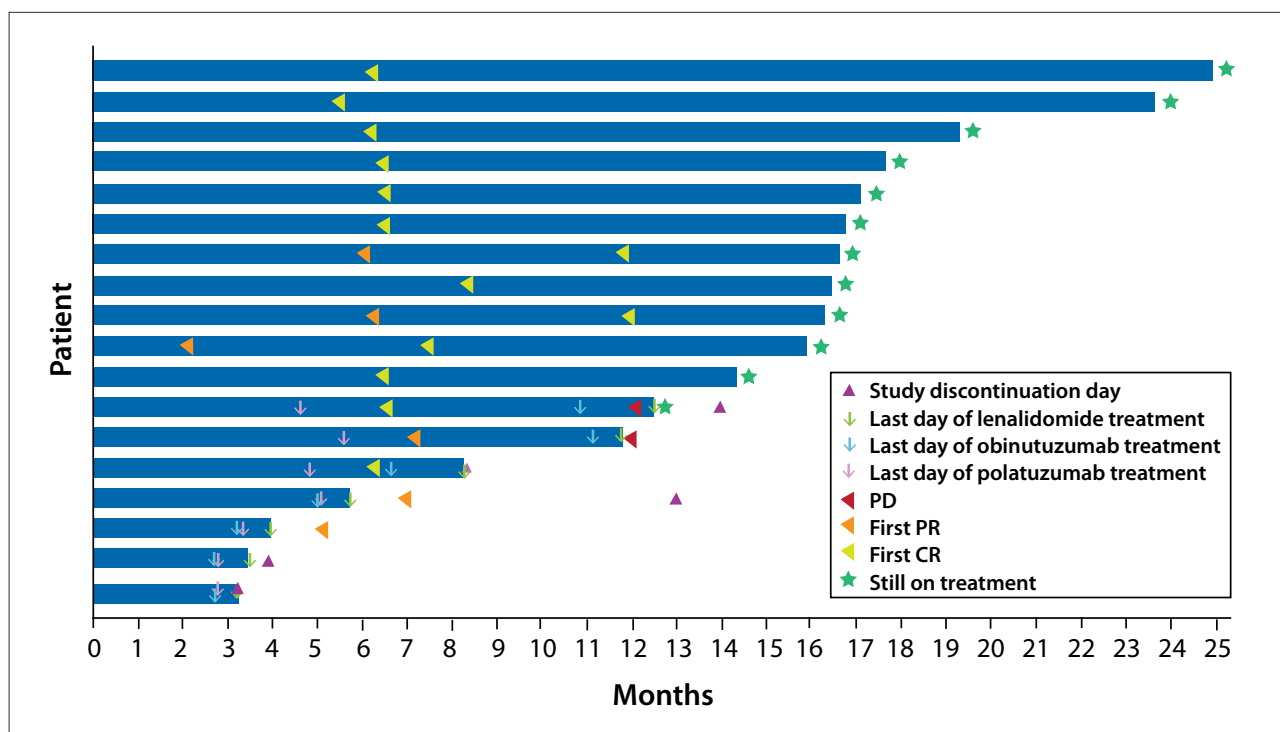


Figure 8. Duration of response among patients with relapsed or refractory follicular lymphoma treated with polatuzumab vedotin plus obinutuzumab and lenalidomide in a phase 1b/2 trial. CR, complete response; PD, progressive disease; PR, partial response. Adapted from Diefenbach C et al. ASCO abstract 7505. *J Clin Oncol.* 2019;37(suppl 15).²

hematologic, renal, or hepatic function; or a positive test for hepatitis.

The interim analysis population consisted of 52 patients who had completed induction therapy and were evaluable for safety. In the dose-escalation portion, 16 patients received treatment at the phase 2 dose. In the dose-expansion portion, 36 patients were treated at the phase 2 dose. Among the patients treated at the recommended phase 2 dose, 18 were evaluable for efficacy.

The patients' median age was 58 years in the efficacy population and 62 years in the safety population. These patients were heavily pretreated; at least 3 prior lines of therapy were reported by 61% of the efficacy population and 58% of the safety population. In each population, 50% of patients were refractory to their most recent prior therapy.

The ORR for the efficacy population was 89%.² The CR by independent review was 67% by modified

Lugano criteria and 78% by Lugano 2014 criteria. The study authors attributed this discrepancy to 3 patients with bone marrow–positive disease who had PET/CT results that were negative at the end of induction, but then did not undergo follow-up bone marrow assessment. According to the modified Lugano criteria, these patients are considered CR unconfirmed and categorized as PRs. An additional 6% of patients had stable disease.

At a median duration of follow-up of 16.6 months, the median PFS was not reached (Figure 8). The 12-month PFS rate was 90%. Among the 17 responders, 2 patients developed disease progression.

In the safety population, grade 3 to 4 AEs occurred in 75% of patients. Most of these events consisted of myelosuppression, particularly neutropenia. Serious AEs were reported in 40% of patients. The most common all-grade AEs were infection (56%),

neutropenia (52%), thrombocytopenia (37%), infusion-related reaction (35%), pyrexia (35%), anemia (33%), diarrhea (29%), and rash (21%). Peripheral neuropathy was reported in 17% of patients, but all cases were grade 1 to 2 and reversible. The most common grade 3/4 AE was neutropenia, occurring in 46% of the safety population. Febrile neutropenia occurred in 4% of patients. In 31% of patients, an AE required a reduction in the dose of lenalidomide. Treatment with lenalidomide was interrupted in 52% of patients and discontinued in 15% owing to AEs.

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First-Line Therapy of T-Cell Lymphoma: Allogeneic or Autologous Transplantation for Consolidation—Final Results of the AATT Study

The prospective, randomized AATT trial (Autologous or Allogeneic Transplantation in T-Cell Lymphoma) evaluated clinical outcomes in patients with T-cell lymphoma who underwent autologous SCT or allogeneic SCT as consolidation therapy. Dr Norbert Schmitz presented the results.¹ The trial recruited more than 100 patients from 44 sites in Germany and France to receive front-line chemotherapy and subsequent consolidation with autologous SCT or allogeneic SCT. Patients who were randomly assigned to autologous SCT underwent peripheral blood stem cell harvest. The study enrolled patients ages 18 to 60 years, with an ECOG performance status between 0 and 3. The most common types of T-cell lymphoma included AITL in 38%, PTCL-NOS in 29%, and anaplastic lymphoma kinase–negative anaplastic

large-cell lymphoma in 14%. The remaining patients had enteropathy type T-cell lymphoma, hepatosplenic T-cell lymphoma, and subcutaneous panniculitis-type T-cell lymphoma.

The hypothesis was that allogeneic SCT would improve 3-year event-free survival from 35% to 60%. The trial design designated enrollment of 140 patients to detect an alpha of 5% with 80% power. A planned interim analysis showed a probability of approximately 10% to detect a difference of 25% in event-free survival, so a data safety monitoring committee stopped the study after accrual of 104 patients.²

Among the 54 patients in the autologous SCT arm, 57% were male. The allogeneic SCT arm had 49 patients, 69% of whom were male.¹ The median age across both treatment arms was 50 years (range, 24-60 years). An elevated lactate dehydrogenase level

was reported in 61% of patients. An ECOG performance status of higher than 1 was seen in 20% of patients, stage III/IV disease was reported in 88%, and 61% had more than 1 extranodal site of disease.

A total of 65% of patients completed the study as per protocol (63% of the autologous SCT arm and 67% of the allogeneic SCT arm). Fifty-eight patients underwent SCT. Among the patients who left the study before SCT, 28% did so because of progressive disease. Notably, 7 patients randomly assigned to allogeneic SCT underwent an autograft transplant. Six of these patients lacked a fully matched donor, and the allogeneic SCT arm was closed before 1 patient could undergo the procedure.

The 3-year rate of event-free survival was 38% in the autologous SCT arm and 43% in the allogeneic SCT

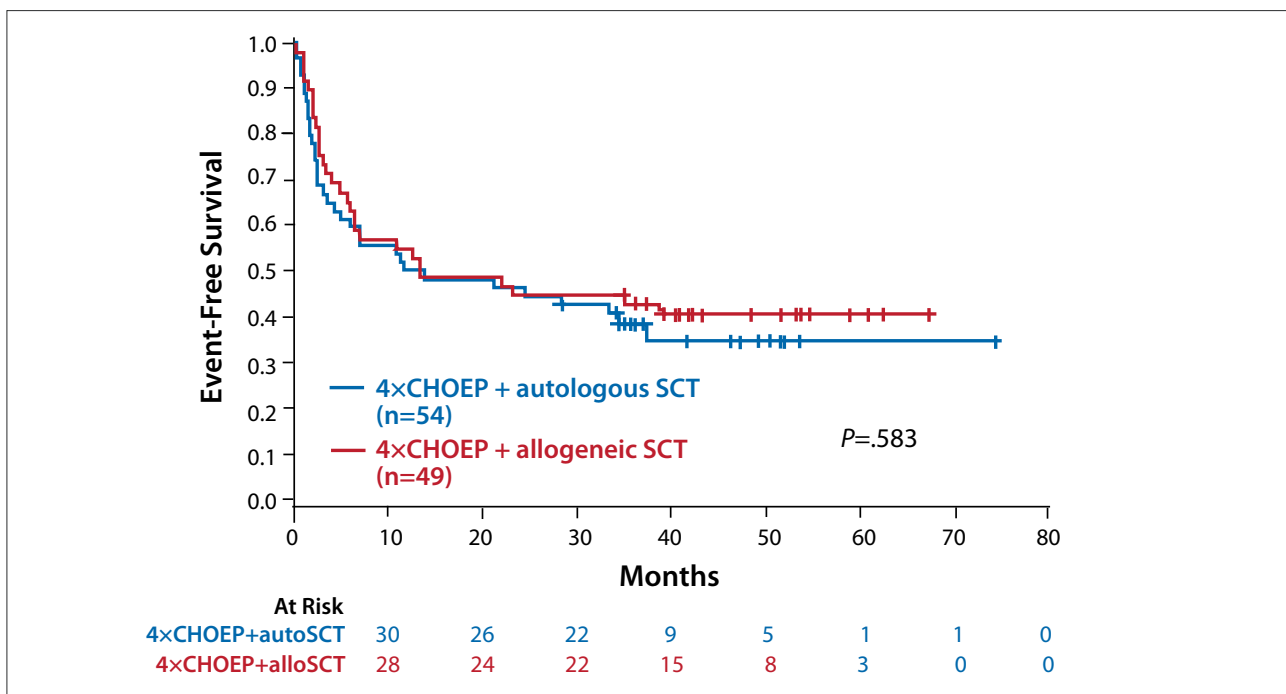


Figure 9. Event-free survival among patients with T-cell lymphoma treated with CHOEP followed by autologous or allogeneic SCT in the AATT trial. AATT, Autologous or Allogeneic Transplantation in T-Cell Lymphoma; alloSCT, allogeneic stem cell transplant; autoSCT, autologous stem cell transplant; CHOEP, cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone; SCT, stem cell transplant. Adapted from Schmitz N et al. ASCO abstract 7503. *J Clin Oncol.* 2019;37(suppl 15).¹

arm, a difference that was not significant ($P=.583$; Figure 9).¹ Among the patients who underwent transplant, the 3-year event-free survival rate was 61% in the autologous SCT arm and 65% in the allogeneic SCT arm, a difference that was also not significant ($P=.430$). Although no significant differences were observed, Dr Schmitz noted that the Kaplan-Meier curve for the patients who underwent allogeneic SCT appeared more stable.

Among the ITT cohort ($n=103$), the rate of 3-year OS was 70% with autologous SCT and 57% with allogeneic SCT, which was not significantly different ($P=.408$).¹ Dr Schmitz suggested that this lack of a significant

difference might be attributed to the fact that one-third of the patients randomly assigned to treatment could not proceed to SCT, in most cases because of refractory disease or early relapse. Significant differences in clinical outcome might have been observed had the analysis been limited to patients who had undergone SCT. The rate of 3-year OS was significantly improved among patients with an International Prognostic Index score of 0 or 1 vs a score of 2 or 3 ($P=.012$).

Across the entire trial, the rate of CR/unconfirmed CR was 45%. This rate was 39% in the autologous SCT arm and 51% in the allogeneic SCT arm. The overall rate of PR was 13%,

with rates of 17% in the autologous arm and 8% in the allogeneic arm. In the ITT population, death from lymphoma was reported in 13 patients vs 11 patients, respectively. Among the 58 patients who underwent SCT, deaths occurred in 8 patients in the autologous group and 9 patients in the allogeneic group.

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Lisocabtagene Maraleucel (Liso-Cel) Treatment of Patients With Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma and Secondary CNS Lymphoma: Initial Results From TRANSCEND NHL 001

The safety and efficacy of lisocabtagene maraleucel were investigated in the phase 1 TRANSCEND-NHL-001 trial (Study Evaluating the Safety and Pharmacokinetics of JCAR017 in B-Cell Non-Hodgkin Lymphoma).¹ The study

enrolled patients with relapsed or refractory NHL with secondary central nervous system lymphoma. They had either DLBCL ($n=8$) treated with at least 2 prior therapies, or mantle cell lymphoma ($n=1$) treated with at least 1 prior therapy.

Following lymphodepletion, patients were treated with lisocabtagene maraleucel at 50×10^6 CAR+ T cells ($n=3$) or 100×10^6 CAR+ T cells ($n=6$). The study permitted a second dose of treatment for patients who developed progressive disease after an initial CR.

Table 1. Summary of Efficacy Among Patients Treated With Lisocabtagene Maraleucel

	Initial Lisocabtagene Maraleucel Infusion ^a (n= 6)	Retreatment ^{a,b} (n=2)	All Patients With DLBCL (n=8)	Patients With MCL (n=1) ^c
Best ORR, ^d n	4	0	4	0
Best CR rate, n	4	0	4	0
Time to CR, median (range)	1.4 (0.9-8.7)	NA	1.4 (0.9-8.7)	NA
PFS, median (95% CI), months	2.9 (0.2-NR)	NA	2.9 (0.2-NR)	NA
OS, median (95% CI), months	10.7 (0.5-NR)	NA	10.7 (0.5-NR)	NA
Follow-up, median, months (95% CI)	24.1 (12.3-24.1)	NA	24.1 (12.3-24.1)	NA
Patients still in response, n	2	0	2	0
Patient deaths (disease progression), n	4	2	6	0

^aIncludes only patients with DLBCL. ^bRetreatment was defined as a second dose of lisocabtagene maraleucel given to patients who achieved a complete response after the first dose of lisocabtagene maraleucel, but who later progressed. ^cBest response was stable disease. ^dBest ORR was considered the response to the dose of lisocabtagene maraleucel that was administered after secondary CNS lymphoma was diagnosed.

CNS, central nervous system; CR, complete response; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; NA, not available; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Adapted from Abramson JS et al. ASCO abstract 7515. *J Clin Oncol*. 2019;37(18 suppl).¹

The patients' median age was 60 years, and they had received a median of 3 lines of prior therapy.¹ The time to peak CAR+ T-cell expansion occurred at a median of 11 days (range, 7-112). Among the 6 patients with DLBCL who received only 1 dose of lisocabtagene maraleucel, best responses included a CR in 4 and progressive disease in 2. Two patients received an additional dose of lisocabtagene maraleucel after progressive disease. The second dose did not lead to an additional response.

The median follow-up was 24.1 months (95% CI, 12.3-24.1) for the 6 patients with DLBCL receiving initial lisocabtagene maraleucel. The median PFS for these patients was 2.9 months (95% CI, 0.2 to not reached; Table 1). The median OS was 10.7 months (95% CI, 0.5 to not reached). Two patients were still in response at the time of the analysis. For the patient with mantle cell lymphoma, the best response was stable disease.

Death from disease progression occurred in 4 patients receiving initial

lisocabtagene maraleucel, and in the 2 patients who received a second course of treatment. All patients in this study developed treatment-emergent AEs, and these events were grade 3 or 4 in most cases. No dose-limiting toxicities occurred, and no patients died from treatment-related causes.

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Rituximab Maintenance for Patients With Diffuse Large B-Cell Lymphoma in First Complete Remission: Results From a Randomized HOVON-Nordic Lymphoma Group Phase III Study

In the phase 3 HOVON 84 NHL trial (Randomized Phase III Study on the Effect of Early Intensification of Rituximab in Combination With 2-Weekly CHOP Chemotherapy Followed by Rituximab Maintenance in Elderly Patients [66-80 Years] With Diffuse Large B-Cell Lymphoma), maintenance with rituximab did not provide an advantage vs observation following induction therapy with rituximab plus CHOP (R-CHOP) in patients with DLBCL.¹ The trial consisted of 2 stages. The first examined rituximab intensification during induction therapy, and showed no benefit in CR or PFS with this approach compared with standard R-CHOP induction therapy.¹⁻³ Throughout the induction stage, the 3-year and 5-year rates of PFS did not differ substantially between the treatments. OS also did not differ between the treatment arms, and no subgroups benefited from rituximab intensification.

The patients in the maintenance stage of the trial had been in a CR for at least 4 weeks following their last cycle of R-CHOP.¹ Patients in the maintenance stage were randomly assigned to an observation arm with no therapy (n=195) or a maintenance arm consisting of intravenous rituximab

given every 8 weeks for 12 doses or until relapse (n=191).^{1,2} In the rituximab maintenance arm, 6 enrolled patients went off-protocol before treatment began. The primary endpoint of

the maintenance stage of the trial was disease-free survival (DFS), based on either relapse or death, measured from the time of randomization to maintenance or observation.

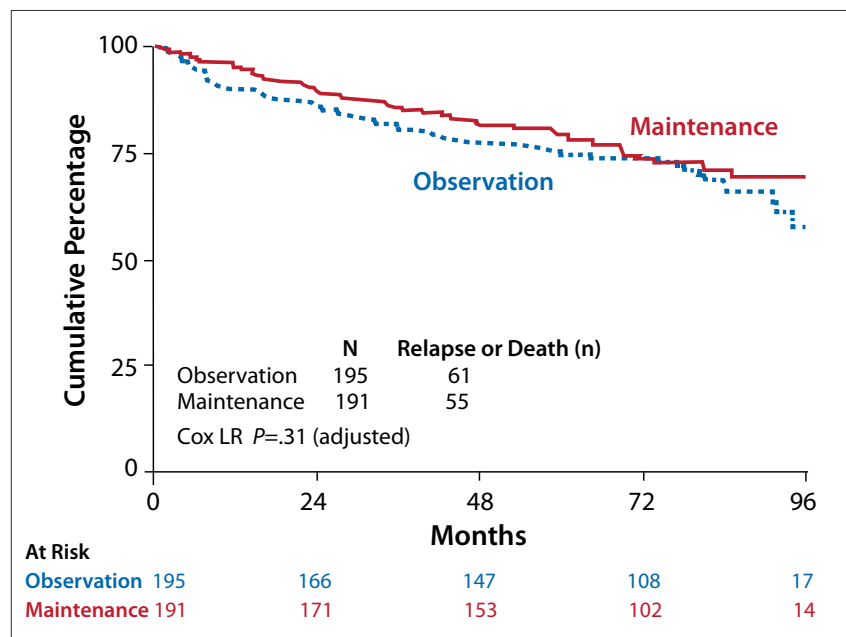


Figure 10. Disease-free survival among patients with DLBCL who received rituximab maintenance or underwent observation in the phase 3 HOVON 84 NHL trial. DLBCL, diffuse large B-cell lymphoma; HOVON 84, Randomized Phase III Study on the Effect of Early Intensification of Rituximab in Combination With 2-Weekly CHOP Chemotherapy Followed by Rituximab Maintenance in Elderly Patients (66-80 Years) With Diffuse Large B-Cell Lymphoma; LR, likelihood ratio. Adapted from Lugtenburg EJ et al. ASCO abstract 7507. *J Clin Oncol*. 2019;37(suppl 15).¹

Patients received rituximab maintenance for a median of 22.5 months. At a median follow-up of 79.9 months, the median DFS was not reached. The 5-year rate of DFS was 79% in patients receiving rituximab maintenance vs 74% in those undergoing observation (HR, 0.83; 95% CI, 0.57-1.19; $P=.31$; Figure 10). Based on competing risk regression analysis, there were also no significant differences in time to relapse (HR, 0.82; 95% CI, 0.52-1.31; $P=.42$) or time to death (HR, 0.87; 95% CI, 0.48-1.59; $P=.66$) between the study arms. Univariate analyses revealed no patient subgroups in which rituximab

maintenance improved DFS. The rate of OS was similar for patients receiving rituximab maintenance or observation (HR, 0.87; 95% CI, 0.57-1.31; $P=.50$).¹ However, the rate of 5-year OS among patients in first CR after R-CHOP was high, at 84%.

A total of 149 patients (81%) completed maintenance therapy with rituximab. Most treatment discontinuations were in response to toxicity ($n=15$) or relapse ($n=14$).¹ Grade 3/4 AEs occurred in 23% of patients who received rituximab maintenance.¹ Serious AEs occurred in 36 patients receiving rituximab (19%); these events were

considered potentially related to the study medication in 15 patients.

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Highlights in Lymphoma From the 2019 American Society of Clinical Oncology Annual Meeting: Commentary

Alex F. Herrera, MD

At the 2019 American Society of Clinical Oncology annual meeting, several presentations provided insight into the management of a range of lymphomas, including non-Hodgkin (NHL) and Hodgkin lymphomas. Studies were presented on stem cell transplant, as well as novel therapies, including antibody-drug conjugates, such as brentuximab vedotin and polatuzumab vedotin; targeted therapies, such as umbralisib and ibrutinib; and immunotherapies, such as sintilimab.

Brentuximab Vedotin

Dr David Straus presented a 3-year follow-up analysis of the ECHELON-1 study.¹ This study compared brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (A+AVD) vs doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) among patients with advanced-stage Hodgkin lymphoma.² The current analysis evaluated standard progression-free survival (PFS), as opposed to the modified PFS that was the primary endpoint of the original study. Modified PFS encompassed the time to progression, death,

or use of subsequent anticancer therapy following less than a complete response. The 3-year analysis also evaluated PFS according to whether the patient's positron emission tomography (PET) scan was positive or negative. The important overall conclusion from the 3-year analysis is that remissions obtained with A+AVD appeared to be durable. At 2 years, the rate of PFS was 84%, compared with 83.1% at 3 years. There were few PFS events during the most recent year of follow-up. Among patients with a negative PET scan at the end of cycle 2 (PET2), the 3-year PFS was 87.2%. A striking finding was that among patients who were PET2-positive and young (<60 years), 3-year traditional PFS was 69.2% in those who continued with A+AVD vs 54.7% among those treated with ABVD. The data from this PET2 analysis are compelling. The outcomes seen with continuation of A+AVD compare favorably with those reported when treatment is changed to escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (escBEACOPP) in patients with a positive PET2 scan after 2 cycles of ABVD,

a strategy used in the S0816 study and the RATHL trial.^{3,4} An appealing aspect of using A+AVD is that it obviates the need for dose escalation to BEACOPP, which is a regimen that can be associated with myelosuppression, infertility, and secondary malignancies.

The ECHELON-2 trial showed a superior outcome with the combination of brentuximab vedotin plus cyclophosphamide, doxorubicin, and prednisone as compared with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).⁵ Dr Ranjana Advani and colleagues analyzed data from this trial to determine the association between response and degree of CD30-positivity in patients with angioimmunoblastic T-cell lymphoma or peripheral T-cell lymphoma (PTCL) not otherwise specified.⁶ The ECHELON-2 study enrolled patients with CD30 expression of 10% or higher. In the analysis by Dr Advani, patients were stratified according to whether their level of CD30 expression was above or below the median.

A previous study of patients with relapsed or refractory T-cell lymphoma showed that CD30 expression did not

correspond to response.⁷ The study by Dr Advani confirmed this finding, showing no association between response and degree of CD30 expression.⁶ These data suggest that patients with CD30 expression of 10% or higher should receive brentuximab vedotin, regardless of the degree of CD30 expression.

Novel Treatments and Regimens

Traditionally, treatments for patients with marginal zone lymphoma (MZL) have been limited to standard chemotherapies. Several novel therapies have been evaluated for patients with MZL. The US Food and Drug Administration recently approved the Bruton tyrosine kinase (BTK) inhibitor ibrutinib for relapsed/refractory disease and lenalidomide combined with rituximab for previously treated MZL.

A study by Dr Felipe Samaniego and coworkers evaluated the phosphoinositide 3-kinase (PI3K) inhibitor umbralisib in relapsed or refractory MZL.⁸ Most patients had received prior chemoimmunotherapy. According to an independent review committee, umbralisib produced an overall response rate of 52%. Stable disease was reported in 36% of patients. Investigator assessment of the interim efficacy population found that the estimated 12-month PFS was 66%.

Overall, umbralisib appeared to have activity in MZL, and the treatment was well tolerated. There was some gastrointestinal toxicity, including diarrhea and nausea, as well as mild myelosuppression. The options for MZL are expanding beyond standard chemoimmunotherapy to include BTK inhibitors and now, potentially, PI3K inhibitors.

Sintilimab is an anti-programmed death 1 (PD-1) antibody developed in China, where it was approved for Hodgkin lymphoma in 2018. Anti-PD-1 antibodies are effective in natural killer/T-cell lymphomas.⁹ A study from Dr Rong Tao evaluated sintilimab in extranodal natural killer/T-

cell lymphoma (ENKTL).¹⁰ This study was performed in Asia, where the incidence of ENKTL is much higher than in the West. In smaller preliminary studies, the anti-PD-1 antibody pembrolizumab was associated with response rates of 57% to 100%.^{11,12} This larger study enrolled 28 patients who had received a median of 3 lines of prior therapy. All patients had received previous treatment with an L-asparaginase-containing regimen. ENKTL is an aggressive disease, and patients with relapsed or refractory disease traditionally have a poor prognosis. In the study by Dr Tao, the overall response rate in patients with relapsed/refractory ENKTL was 68%, which is a promising outcome in this high-risk population.¹⁰ The disease control rate was 86%. The rate of 1-year overall survival was 82%, and the median overall survival was not reached. As a comparison, the study authors cited a median overall survival of 4.8 months in a retrospective Chinese study of 46 patients with relapsed/refractory ENKTL treated with various standard salvage chemotherapy regimens.¹⁰ In the study by Dr Tao, benefits were more pronounced among patients with nodal disease, rather than bone marrow involvement, with excellent survival in this subgroup. The side effect profile of sintilimab was consistent with that of other anti-PD-1 antibodies. This larger study confirmed that most patients with relapsed/refractory ENKTL respond to PD-1 blockade.

A study presented by Dr Catherine Diefenbach evaluated polatuzumab vedotin, obinutuzumab, and lenalidomide in patients with relapsed or refractory follicular lymphoma.¹³ Lenalidomide is an effective therapy for the treatment of patients with previously untreated or relapsed/refractory follicular lymphoma. A recent study showed similar outcomes with first-line chemoimmunotherapy vs rituximab plus lenalidomide in the first-line treatment of follicular lymphoma.¹⁴ Studies have also demonstrated that the combination of lenalidomide

plus obinutuzumab was effective in patients with follicular lymphoma.¹⁵ In the study by Dr Diefenbach, most patients had advanced-stage disease, had received 3 or more prior lines of treatment, and were refractory to their most recent prior therapy.¹³

Among the 18 patients treated, the early data on efficacy were promising, with a complete response rate of 78% and an overall response rate of 89% according to the 2014 Lugano classification.¹³ After a median follow-up of 16 months, 2 of 17 patients who responded to treatment had developed disease progression. The 12-month rate of PFS was 90%. These data are preliminary, but promising for a group of patients who were mostly refractory to their last treatment and had received a median of 3 prior lines of therapy.

The combination regimen did not show any unexpected safety signals. The most common side effects were neutropenia and thrombocytopenia, which were expected because lenalidomide and polatuzumab vedotin are each associated with cytopenias. Infections were relatively common. There were some gastrointestinal toxicities, including diarrhea. Infusion-related reactions were seen, as would be expected with obinutuzumab. Grade 3 or 4 adverse events were primarily hematologic; neutropenia was the most common.

Dr Jason Westin presented results of the Smart Start study, which evaluated lead-in treatment with rituximab, lenalidomide, and ibrutinib, following by administration of this triplet in combination with chemotherapy, among patients with newly diagnosed non-germinal center B-cell subtype (non-GCB) diffuse large B-cell lymphoma (DLBCL).¹⁶ Patients with non-GCB DLBCL typically have poorer outcomes after standard R-CHOP treatment. The response rate after the lead-in period with the triplet of rituximab, lenalidomide, and ibrutinib was 86%, with a complete response rate of nearly 40%. At the end of treatment with the triplet plus chemotherapy,

among 49 evaluable patients, the complete response rate was 96%, which is very high for patients with non-GCB DLBCL. Among the 19 patients with double-expresser DLBCL, PFS was 94% at 1 year.

After 1 year of follow-up, there were 3 progression events. More time will be needed to assess the long-term durability of the excellent responses to this regimen. One patient who had received corticosteroids before starting the triplet lead-in regimen developed central nervous system aspergillosis. A study amendment then prohibited the prephase use of corticosteroids, and no other fungal infections were seen. There were no major toxicity signals, aside from rash, which is known to occur with the combination of lenalidomide and ibrutinib. There was a reasonably high rate of grade 4 neutropenia, which could be expected given that chemotherapy was combined with lenalidomide and ibrutinib, which are both associated with myelosuppression. Febrile neutropenia occurred in nearly one-quarter of patients, a higher rate than might be expected with standard chemotherapy. Therefore, the promising outcomes corresponded to some degree of increased toxicity. However, these results are extremely promising, and they could potentially inform the design of a larger, more definitive study. Results from longer-term follow-up are eagerly awaited.

Allogeneic vs Autologous Transplant

A randomized study presented by Dr Norbert Schmitz compared allogeneic vs autologous transplant as frontline therapy for younger patients with PTCL, a lymphoma subtype associated with a poor prognosis.¹⁷ Patients first received 4 cycles of CHOP plus etoposide. They then received 1 cycle of dexamethasone, cytarabine, and cisplatin. Patients who were randomly assigned to autologous transplant underwent harvesting for stem cells. Patients who were randomly assigned to allogeneic transplant proceeded to

treatment. An important issue with this study concerns the selection of myeloablative conditioning for the patients undergoing allogeneic stem cell transplant. In recent years, reduced-intensity conditioning has been increasingly utilized in patients with NHL. Rates of event-free survival were similar between the arms in the intention-to-treat population. Among the patients who underwent transplant, there was no statistically significant difference in the rates of event-free survival or overall survival between the treatments. Transplant-related mortality reached 16% in the allogeneic transplant arm vs 0% in the autologous arm. The number of deaths from lymphoma was similar in both groups. There were more cases of relapsed disease in the autologous group vs the allogeneic group, but this difference was mitigated by the higher rates of transplant-related morbidity and mortality in the allogeneic transplant group. For patients with PTCL who respond to initial therapy, the typical treatment has been consolidative autologous stem-cell transplant in patients who achieved a first response. This study confirmed this practice, showing that the morbidity and mortality associated with allogeneic stem-cell transplant are unacceptably high, without a concomitant improvement in outcomes in this setting.

Disclosure

Dr Herrera is a consultant for Bristol-Myers Squibb, Genentech, Merck & Co, Kite Pharma/Gilead, Seattle Genetics, and Adaptive Biotechnologies. Dr Herrera has received research funding/grants from Genentech, Bristol-Myers Squibb, Immune Design, AstraZeneca, Merck & Co, Pharmacyclics, Seattle Genetics, Kite Pharma, and Gilead Sciences.

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