

A SPECIAL MEETING REVIEW EDITION

Highlights in Lymphoma From the 2017 American Society of Clinical Oncology Annual Meeting and the 14th International Conference on Malignant Lymphoma

A Review of Selected Presentations From the 2017 ASCO Annual Meeting • June 2-6, 2017
• Chicago, Illinois and the 14th ICML • June 14-17, 2017 • Lugano, Switzerland

Special Reporting on:

- Baseline Metabolic Tumor Volume Is an Independent Prognostic Factor for Relapsed and Refractory Hodgkin Lymphoma Patients Receiving PET-Adapted Salvage Therapy With Brentuximab Vedotin and Augmented ICE
- Copanlisib in Patients With Relapsed or Refractory Indolent B-Cell Lymphoma (CHRONOS-1)
- Brentuximab Vedotin in Combination With Nivolumab in Patients With Relapsed or Refractory Hodgkin Lymphoma
- CR Rates in Relapsed/Refractory Aggressive B-NHL Treated With the CD19-Directed CAR T-Cell Product JCAR017 (TRANSCEND NHL 001)
- Outcomes by CD30 Expression in Patients With CTCL Receiving Brentuximab Vedotin Vs Physician's Choice in the Phase 3 ALCANZA Study
- Bendamustine Plus Rituximab Versus CHOP Plus Rituximab as First-Line Treatment in Patients With Indolent Lymphomas: Nine-Year Updated Results From the StiL NHL1 Study
- Results of a Phase II Study of Brentuximab Vedotin in the First-Line Treatment of Hodgkin Lymphoma Patients Considered Unsuited for Standard Chemotherapy (BREVITY)
- First-Line Treatment of iNHL or MCL Patients With BR or R-CHOP/R-CVP: Results of the BRIGHT 5-Year Follow-Up Study
- Brentuximab Vedotin Consolidation to Reduce Radiation Use in Patients With Limited Stage Non-Bulky Hodgkin Lymphoma: an Update From a Phase 2 Clinical Trial

PLUS Meeting Abstract Summaries

With Expert Commentary by:

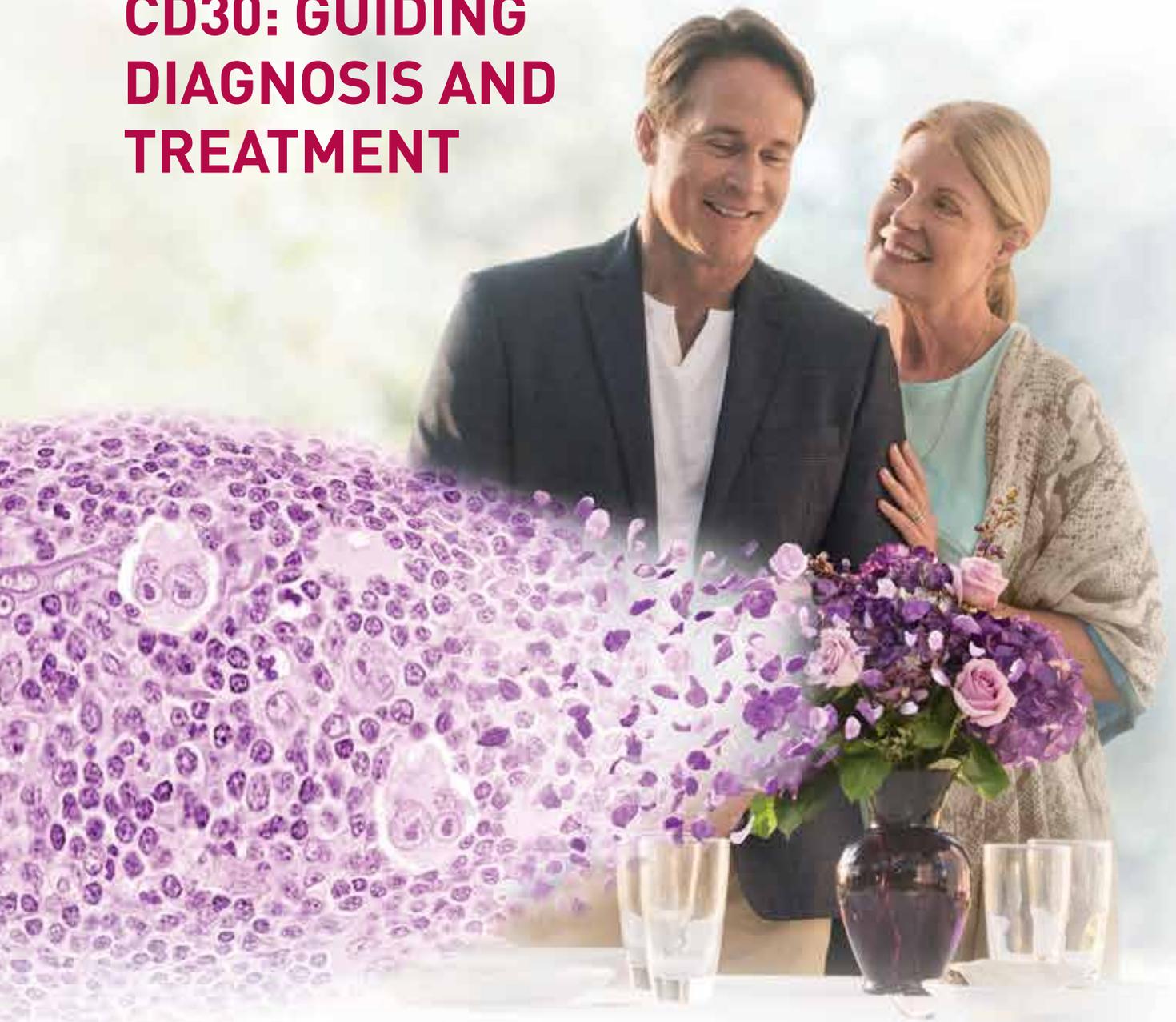
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Early and accurate testing

CD30: GUIDING DIAGNOSIS AND TREATMENT



ADCETRIS® (brentuximab vedotin) is an antibody-drug conjugate designed to target cells expressing CD30. CD30 is expressed on the surface of sALCL cells and Reed-Sternberg cells in classical HL, with limited expression on healthy tissue and cells.¹ Consensus guidelines recommend CD30 IHC testing for the diagnosis of classical HL and sALCL.²⁻⁵

Incorporating CD30 IHC early in the diagnostic process may ensure accurate diagnosis and appropriate treatment selection.⁶

Indications

ADCETRIS is indicated for treatment of patients with:

- Classical Hodgkin lymphoma (HL) after failure of autologous hematopoietic stem cell transplantation (auto-HSCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates.¹
- Classical HL at high risk of relapse or progression as post-auto-HSCT consolidation.¹
- Systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen.¹

The sALCL indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.¹

Important Safety Information

BOXED WARNING

Progressive multifocal leukoencephalopathy (PML): JC virus infection resulting in PML and death can occur in patients receiving ADCETRIS.

Contraindication:

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

Warnings and Precautions:

- **Peripheral neuropathy (PN):** ADCETRIS treatment causes a PN that is predominantly sensory. Cases of motor PN have also been reported. ADCETRIS-induced PN is cumulative. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness and institute dose modifications accordingly.
- **Anaphylaxis and infusion reactions:** Infusion-related reactions, including anaphylaxis, have occurred with ADCETRIS. Monitor patients during infusion. If an infusion-related reaction occurs, interrupt the infusion and institute appropriate medical management. If anaphylaxis occurs, immediately and permanently discontinue the infusion and administer appropriate medical therapy. Patients who experienced a prior infusion-related reaction should be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.
- **Hematologic toxicities:** Prolonged (≥ 1 week) severe neutropenia and Grade 3 or 4 thrombocytopenia or anemia can occur with ADCETRIS. Febrile neutropenia has been reported with ADCETRIS. Monitor complete blood counts prior to each dose of ADCETRIS and consider more frequent monitoring 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 patients treated with ADCETRIS. Closely monitor patients during treatment for the emergence of possible 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 the use of ADCETRIS 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 the use of ADCETRIS in patients with moderate or severe hepatic impairment.
- **Hepatotoxicity:** Serious cases of hepatotoxicity, including fatal outcomes, have occurred with ADCETRIS. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, and occurred after the first dose of ADCETRIS or 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.
- **Progressive multifocal leukoencephalopathy (PML):** JC virus infection resulting in PML and death has 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 if PML is suspected and discontinue ADCETRIS if PML is confirmed.
- **Pulmonary toxicity:** Events of noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome, some with fatal outcomes, 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.
- **Serious dermatologic reactions:** Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), including fatal outcomes, have been reported with ADCETRIS. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.
- **Gastrointestinal (GI) complications:** Fatal and serious GI complications, including perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, neutropenic colitis, and ileus have been reported in ADCETRIS-treated patients. Lymphoma with preexisting GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, perform a prompt diagnostic evaluation and treat appropriately.
- **Embryo-fetal toxicity:** Based on the mechanism of action and findings in animals, ADCETRIS can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Adverse Reactions:

In two uncontrolled single-arm trials of ADCETRIS as monotherapy in 160 patients with relapsed classical HL and sALCL, the most common adverse reactions ($\geq 20\%$), regardless of causality, were: neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough and vomiting.

In a placebo-controlled trial of ADCETRIS in 329 patients with classical HL at high risk of relapse or progression post auto-HSCT, the most common adverse reactions ($\geq 20\%$) in the ADCETRIS-treatment arm (167 patients), regardless of causality, were: neutropenia, peripheral sensory neuropathy, thrombocytopenia, anemia, upper respiratory tract infection, fatigue, peripheral motor neuropathy, nausea, cough, and diarrhea.

Drug Interactions:

Concomitant use of strong CYP3A4 inhibitors or inducers, or P-gp inhibitors, has the potential to affect the exposure to monomethyl auristatin E (MMAE).

Use in Specific Populations:

MMAE exposure and adverse reactions are increased in patients with moderate or severe hepatic impairment or severe renal impairment. Avoid use.

Advise females of reproductive potential 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 and avoid breastfeeding while receiving ADCETRIS.

Please see brief summary of Prescribing Information on following pages and full Prescribing Information at ADCETRIS.com.

References: 1. ADCETRIS [prescribing information]. Bothell, WA: Seattle Genetics, Inc., 2016. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) for Hodgkin Lymphoma (V.1.2017). ©National Comprehensive Cancer Network, Inc. 2017. All rights reserved. Accessed March 1, 2017. To view the most recent and complete version of the guidelines, go to www.nccn.org. 3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) for T-cell Lymphomas (V.2.2017). ©National Comprehensive Cancer Network, Inc. 2017. All rights reserved. Accessed March 1, 2017. To view the most recent and complete version of the guidelines, go to www.nccn.org. 4. College of American Pathologists. Protocol for the examination of specimens from patients with Hodgkin lymphoma. v3.1.0.0. Updated October 2013. 5. College of American Pathologists. Protocol for the examination of specimens from patients with non-Hodgkin lymphoma/lymphoid neoplasms. v3.2.0.0. Updated October 2013. 6. Hsi ED, Said J, Macon WR, et al. Diagnostic accuracy of a defined immunophenotypic and molecular genetic approach for peripheral T/NK-cell lymphomas: a North American PTCL study group project. *Am J Surg Pathol*. 2014;38:768-775. 7. Data on file. Seattle Genetics, Inc.

*ADCETRIS was first approved for use in 2011.



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BACKED BY EXPERIENCE

OVER 10,000
PATIENTS TREATED
SINCE APPROVAL^{*7}



CD30-DIRECTED

ADCETRIS[®]

brentuximab vedotin | for injection

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

Brief Summary: see package insert for complete 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 treatment of patients with:

1.1 Classical Hodgkin Lymphoma (HL)

Classical HL after failure of autologous hematopoietic stem cell transplantation (auto-HSCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates.

1.2 Classical Hodgkin Lymphoma (HL) Post-auto-HSCT Consolidation

Classical HL at high risk of relapse or progression as post-auto-HSCT consolidation.

1.3 Systemic Anaplastic Large Cell Lymphoma (sALCL)

sALCL after failure of at least one prior multi-agent chemotherapy regimen.

The sALCL indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Recommendations

Administer ADCETRIS as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

For classical HL post-auto-HSCT consolidation treatment, initiate ADCETRIS treatment within 4–6 weeks post-auto-HSCT or upon recovery from auto-HSCT. These patients should continue treatment until a maximum of 16 cycles, disease progression, or unacceptable toxicity.

The recommended dose is 1.8 mg/kg up to 180 mg. Reduce the dose in patients with mild hepatic impairment (Child-Pugh A) to 1.2 mg/kg up to 120 mg. Avoid use in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or severe renal impairment (creatinine clearance <30 mL/min).

2.2 Dose Modification

Peripheral Neuropathy: For new or worsening Grade 2 or 3 neuropathy, dosing should be held until neuropathy improves to Grade 1 or baseline and then restarted at 1.2 mg/kg. For Grade 4 peripheral neuropathy, ADCETRIS should be discontinued.

Neutropenia: The dose of ADCETRIS should be held for Grade 3 or 4 neutropenia until resolution to baseline or Grade 2 or lower. Consider G-CSF prophylaxis for subsequent cycles in patients who experience Grade 3 or 4 neutropenia in the previous cycle. In patients with recurrent Grade 4 neutropenia despite the use of G-CSF prophylaxis, consider discontinuation or dose reduction of ADCETRIS to 1.2 mg/kg.

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 the relapsed classical HL and sALCL clinical trials, 54% of patients experienced any grade of neuropathy. Of these patients, 49% had complete resolution, 31% had partial improvement, and 20% had no improvement. Of the patients who reported neuropathy, 51% had residual neuropathy at the time of their last evaluation. 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, the infusion should be interrupted and appropriate medical management instituted. 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

Prolonged (≥ 1 week) severe neutropenia and Grade 3 or Grade 4 thrombocytopenia or anemia can occur with ADCETRIS. Febrile neutropenia has been reported with treatment with ADCETRIS. Complete blood counts should be monitored prior to each dose of ADCETRIS and more frequent monitoring should be considered 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. Patients should be closely monitored 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 [creatinine clearance (CLcr) <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

Serious cases of hepatotoxicity, including fatal outcomes, 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

JC virus infection resulting in PML and death has 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

Events of noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome (ARDS), some with fatal outcomes, 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

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), including fatal outcomes, have been reported with ADCETRIS. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.

5.12 Gastrointestinal Complications

Fatal and serious gastrointestinal (GI) complications including perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, neutropenic colitis, and ileus have been reported in ADCETRIS-treated patients. Lymphoma with preexisting GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, perform a prompt diagnostic evaluation and treat appropriately.

5.13 Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, ADCETRIS can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of ADCETRIS in pregnant women. Brentuximab vedotin caused embryo-fetal toxicities, including significantly decreased embryo viability and fetal malformations, in animals at maternal exposures that were similar to the clinical dose of 1.8 mg/kg every three weeks. Advise females of reproductive potential to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS. If ADCETRIS is used during pregnancy or if the patient becomes pregnant during ADCETRIS treatment, the patient should be apprised of the potential risk to the fetus.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

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

The data below reflect exposure to ADCETRIS as monotherapy in 327 patients with classical Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL), including 160 patients in two uncontrolled single-arm trials (Studies 1 and 2) and 167 patients in one placebo-controlled randomized trial (Study 3).

In Studies 1 and 2, the most common adverse reactions ($\geq 20\%$), regardless of causality, were neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough, and vomiting. The most common adverse reactions occurring in at least 10% of patients in either Study 1 or 2, regardless of causality, using the NCI Common Toxicity Criteria (CTC) Version 3.0, are shown in Table 1.

In Study 3, the most common adverse reactions ($\geq 20\%$) in the ADCETRIS-treatment arm, regardless of causality, were neutropenia, peripheral sensory neuropathy, thrombocytopenia, anemia, upper respiratory tract infection, fatigue, peripheral motor neuropathy, nausea, cough, and diarrhea. The most common adverse reactions occurring in at least 10% of patients, using the NCI CTC Version 4, are shown in Table 2.

Experience in Classical Hodgkin Lymphoma

Summary of Clinical Trial Experience in Relapsed Classical HL (Study 1)

ADCETRIS was studied in 102 patients with classical HL in a single arm clinical trial in which the recommended starting dose and schedule was 1.8 mg/kg intravenously every 3 weeks. Median duration of treatment was 9 cycles (range, 1–16).

The most common adverse reactions ($\geq 20\%$), regardless of causality, were neutropenia, peripheral sensory neuropathy, fatigue, upper respiratory tract infection, nausea, diarrhea, anemia, pyrexia, thrombocytopenia, rash, abdominal pain, cough, and vomiting.

Summary of Clinical Trial Experience in Classical HL Post-auto-HSCT Consolidation (Study 3)

ADCETRIS was studied in 329 patients with classical HL at high risk of relapse or progression post-auto-HSCT in a randomized, double-blind, placebo-controlled clinical trial in which the recommended starting dose and schedule was 1.8 mg/kg of ADCETRIS administered intravenously over 30 minutes every 3 weeks or placebo for up to 16 cycles. Of the 329 enrolled patients, 327 (167 brentuximab vedotin, 160 placebo) received at least one dose of study treatment. The median number of treatment cycles in each study arm was 15 (range, 1–16) and 80 patients (48%) in the ADCETRIS-treatment arm received 16 cycles.

Standard international guidelines were followed for infection prophylaxis for herpes simplex virus (HSV), varicella-zoster virus (VZV), and Pneumocystis jiroveci pneumonia (PCP) post-auto-HSCT. Overall, 312 patients (95%) received HSV and VZV prophylaxis with a median duration of 11.1 months (range, 0–20) and 319 patients (98%) received PCP prophylaxis with a median duration of 6.5 months (range, 0–20).

Experience in Systemic Anaplastic Large Cell Lymphoma

Summary of Clinical Trial Experience in Relapsed sALCL (Study 2)

ADCETRIS was studied in 58 patients with sALCL in a single arm clinical trial in which the recommended starting dose and schedule was 1.8 mg/kg intravenously every 3 weeks. Median duration of treatment was 7 cycles (range, 1–16).

The most common adverse reactions ($\geq 20\%$), regardless of causality, were neutropenia, anemia, peripheral sensory neuropathy, fatigue, nausea, pyrexia, rash, diarrhea, and pain.

Table 1: Most Commonly Reported ($\geq 10\%$) Adverse Reactions in Studies 1 and 2

Adverse Reaction	Classical HL % of patients (Total N=102)			sALCL % of patients (Total N=58)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
<i>Blood and lymphatic system disorders</i>						
Neutropenia*	54	15	6	55	12	9
Anemia*	33	8	2	52	2	-
Thrombocytopenia*	28	7	2	16	5	5
Lymphadenopathy	11	-	-	10	-	-
<i>Nervous system disorders</i>						
Peripheral sensory neuropathy	52	8	-	53	10	-
Peripheral motor neuropathy	16	4	-	7	3	-
Headache	19	-	-	16	2	-
Dizziness	11	-	-	16	-	-
<i>General disorders and administration site conditions</i>						
Fatigue	49	3	-	41	2	2
Pyrexia	29	2	-	38	2	-
Chills	13	-	-	12	-	-
Pain	7	-	-	28	-	5
Edema peripheral	4	-	-	16	-	-

*Derived from laboratory values and adverse reaction data

Adverse Reaction	Classical HL % of patients (Total N=102)			sALCL % of patients (Total N=58)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
<i>Infections and infestations</i>						
Upper respiratory tract infection	47	-	-	12	-	-
<i>Gastrointestinal disorders</i>						
Nausea	42	-	-	38	2	-
Diarrhea	36	1	-	29	3	-
Abdominal pain	25	2	1	9	2	-
Vomiting	22	-	-	17	3	-
Constipation	16	-	-	19	2	-
<i>Skin and subcutaneous tissue disorders</i>						
Rash	27	-	-	31	-	-
Pruritus	17	-	-	19	-	-
Alopecia	13	-	-	14	-	-
Night sweats	12	-	-	9	-	-
Dry skin	4	-	-	10	-	-
<i>Respiratory, thoracic and mediastinal disorders</i>						
Cough	25	-	-	17	-	-
Dyspnea	13	1	-	19	2	-
Oropharyngeal pain	11	-	-	9	-	-
<i>Musculoskeletal and connective tissue disorders</i>						
Arthralgia	19	-	-	9	-	-
Myalgia	17	-	-	16	2	-
Back pain	14	-	-	10	2	-
Pain in extremity	10	-	-	10	2	2
Muscle spasms	9	-	-	10	2	-
<i>Psychiatric disorders</i>						
Insomnia	14	-	-	16	-	-
Anxiety	11	2	-	7	-	-
<i>Metabolism and nutrition disorders</i>						
Decreased appetite	11	-	-	16	2	-
<i>Investigations</i>						
Weight decreased	6	-	-	12	3	-

Table 2: Most Commonly Reported ($\geq 10\%$ in the ADCETRIS arm) Adverse Reactions in Study 3

Adverse Reaction	ADCETRIS % of patients (Total N=167)			Placebo % of patients (Total N=160)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
<i>Blood and lymphatic system disorders</i>						
Neutropenia*	78	30	9	34	6	4
Thrombocytopenia*	41	2	4	20	3	2
Anemia*	27	4	-	19	2	-
<i>Nervous system disorders</i>						
Peripheral sensory neuropathy	56	10	-	16	1	-
Peripheral motor neuropathy	23	6	-	2	1	-
Headache	11	2	-	8	1	-

*Derived from laboratory values and adverse reaction data

Adverse Reaction	ADCETRIS % of patients (Total N=167)			Placebo % of patients (Total N=160)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
<i>Infections and infestations</i>						
Upper respiratory tract infection	26	-	-	23	1	-
<i>General disorders and administration site conditions</i>						
Fatigue	24	2	-	18	3	-
Pyrexia	19	2	-	16	-	-
Chills	10	-	-	5	-	-
<i>Gastrointestinal disorders</i>						
Nausea	22	3	-	8	-	-
Diarrhea	20	2	-	10	1	-
Vomiting	16	2	-	7	-	-
Abdominal pain	14	2	-	3	-	-
Constipation	13	2	-	3	-	-
<i>Respiratory, thoracic and mediastinal disorders</i>						
Cough	21	-	-	16	-	-
Dyspnea	13	-	-	6	-	1
<i>Investigations</i>						
Weight decreased	19	1	-	6	-	-
<i>Musculoskeletal and connective tissue disorders</i>						
Arthralgia	18	1	-	9	-	-
Muscle spasms	11	-	-	6	-	-
Myalgia	11	1	-	4	-	-
<i>Skin and subcutaneous tissue disorders</i>						
Pruritus	12	1	-	8	-	-
<i>Metabolism and nutrition disorders</i>						
Decreased appetite	12	1	-	6	-	-

Additional Important Adverse Reactions

Peripheral neuropathy

In Studies 1 and 2, 54% of patients experienced any grade of neuropathy. Of these patients, 49% had complete resolution, 31% had partial improvement, and 20% had no improvement. Of the patients who reported neuropathy, 51% had residual neuropathy at the time of their last evaluation.

In Study 3, 67% of patients treated with ADCETRIS experienced any grade of neuropathy. The median time to first onset of any grade was 14 weeks (range, 0.1–47), of Grade 2 was 27 weeks (range, 0.4–52) and of Grade 3 was 34 weeks (range, 7–106). The median time from onset to resolution or improvement of any grade was 23 weeks (range, 0.1–138), of Grade 2 was 24 weeks (range, 1–108), and of Grade 3 was 25 weeks (range, 2–98). Of the patients who reported neuropathy, 59% had complete resolution and 41% had residual neuropathy (26% partial improvement, 15% no improvement) at the time of their last evaluation.

Infusion reactions

Two cases of anaphylaxis were reported in the dose-finding trials. There were no Grade 3 or 4 infusion-related reactions reported in Studies 1 and 2; however, Grade 1 or 2 infusion-related reactions were reported for 19 patients (12%). In Studies 1 and 2, the most common adverse reactions ($\geq 2\%$) associated with infusion-related reactions were chills (4%), nausea (3%), dyspnea (3%), pruritus (3%), pyrexia (2%), and cough (2%).

In Study 3, infusion-related reactions were reported in 25 patients (15%) in the ADCETRIS-treated arm and 3 patients (2%) in the placebo arm. Grade 3 events were reported in 3 of the 25 patients treated with ADCETRIS who experienced infusion-related reactions. No Grade 4 infusion-related reactions were reported. The most common adverse reactions ($\geq 2\%$) associated with infusion-related reactions were nausea (4%), chills (4%), dyspnea (2%), headache (2%), pruritus (2%), rash (2%), back pain (2%), and vomiting (2%).

Pulmonary Toxicity

In a trial in patients with classical HL 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 (adriamycin, 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.

Cases of pulmonary toxicity have also been reported in patients receiving ADCETRIS. In Study 3, pulmonary toxicity was reported in 8 patients (5%) in the ADCETRIS-treated arm and 5 patients (3%) in the placebo arm. A causal association with single-agent ADCETRIS has not been established.

Serious adverse reactions

In Studies 1 and 2, serious adverse reactions, regardless of causality, were reported in 31% of patients receiving ADCETRIS. The most common serious adverse reactions experienced by patients with classical HL include peripheral motor neuropathy (4%), abdominal pain (3%), pulmonary embolism (2%), pneumonitis (2%), pneumothorax (2%), pyelonephritis (2%), and pyrexia (2%). The most common serious adverse reactions experienced by patients with sALCL were septic shock (3%), supraventricular arrhythmia (3%), pain in extremity (3%), and urinary tract infection (3%). Other important serious adverse reactions reported include PML, Stevens-Johnson syndrome, and tumor lysis syndrome.

In Study 3, serious adverse reactions, regardless of causality, were reported in 25% of ADCETRIS-treated patients. The most common serious adverse reactions were pneumonia (4%), pyrexia (4%), vomiting (3%), nausea (2%), hepatotoxicity (2%), and peripheral sensory neuropathy (2%).

Dose modifications

Adverse reactions that led to dose delays in more than 5% of patients in Studies 1 and 2 were neutropenia (14%) and peripheral sensory neuropathy (11%).

Adverse reactions that led to dose delays in more than 5% of ADCETRIS-treated patients in Study 3 were neutropenia (22%), peripheral sensory neuropathy (16%), upper respiratory tract infection (6%), and peripheral motor neuropathy (6%).

Discontinuations

Adverse reactions led to treatment discontinuation in 21% of patients in Studies 1 and 2. Adverse reactions that led to treatment discontinuation in 2 or more patients with classical HL or sALCL were peripheral sensory neuropathy (8%) and peripheral motor neuropathy (3%).

Adverse reactions led to treatment discontinuation in 32% of ADCETRIS-treated patients in Study 3. Adverse reactions that led to treatment discontinuation in 2 or more patients were peripheral sensory neuropathy (14%), peripheral motor neuropathy (7%), acute respiratory distress syndrome (1%), paraesthesia (1%), and vomiting (1%).

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:

- Pancreatitis (including fatal outcomes). Consider the diagnosis of pancreatitis for patients presenting with severe abdominal pain.
- 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

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

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to ADCETRIS with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on ADCETRIS

CYP3A4 Inhibitors/Inducers: In vitro data indicate that monomethyl auristatin E (MMAE) is a substrate of CYP3A4/5. MMAE is primarily metabolized by CYP3A. Co-administration of ADCETRIS with ketoconazole, a potent CYP3A4 inhibitor, increased exposure to MMAE by approximately 34%. Patients who are receiving strong CYP3A4 inhibitors concomitantly with ADCETRIS should be closely monitored for adverse reactions. Co-administration of ADCETRIS with rifampin, a potent CYP3A4 inducer, reduced exposure to MMAE by approximately 46%.

P-gp Inhibitors: In vitro data indicate that MMAE is a substrate of the efflux transporter P-glycoprotein (P-gp). Co-administration of ADCETRIS with P-gp inhibitors may increase exposure to MMAE. Patients who are receiving P-gp inhibitors concomitantly with ADCETRIS should be closely monitored for adverse reactions.

7.2 Effect of ADCETRIS on Other Drugs

In vitro data indicate that MMAE is an inhibitor of CYP3A4/5. Co-administration of ADCETRIS did not affect exposure to midazolam, a CYP3A4 substrate. MMAE does not inhibit other CYP enzymes at relevant clinical concentrations. ADCETRIS is not expected to alter the exposure to drugs that are metabolized by CYP3A4 enzymes.

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]. Consider the benefits and risks of ADCETRIS and possible risks to the fetus when prescribing ADCETRIS to a pregnant woman.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Data

Animal Data

In an embryo-fetal developmental study, pregnant rats received 2 intravenous doses of 0.3, 1, 3, or 10 mg/kg brentuximab vedotin during the period of organogenesis (once each on Pregnancy Days 6 and 13). Drug-induced embryo-fetal toxicities were seen mainly in animals treated with 3 and 10 mg/kg of the drug and included increased early resorption ($\geq 99\%$), post-implantation loss ($\geq 99\%$), decreased numbers of live fetuses, and external malformations (i.e., umbilical hernias and malrotated hindlimbs). Systemic exposure in animals at the brentuximab vedotin dose of 3 mg/kg is approximately the same exposure in patients with classical HL or sALCL who received the recommended dose of 1.8 mg/kg every three weeks.

8.2 Lactation

There is no information regarding the presence of brentuximab vedotin in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed infant 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

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

Clinical trials of ADCETRIS did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

8.6 Renal Impairment

Avoid the use of ADCETRIS in patients with severe renal impairment (CL_{cr} <30 mL/min).

The kidney is a route of excretion for monomethyl auristatin E (MMAE). The pharmacokinetics and safety of brentuximab vedotin and MMAE were evaluated after the administration of 1.2 mg/kg of ADCETRIS to patients with mild (CL_{cr} >50–80 mL/min; n=4), moderate (CL_{cr} 30–50 mL/min; n=3) and severe (CL_{cr} <30 mL/min; n=3) renal

impairment. In patients with severe renal impairment, the rate of Grade 3 or worse adverse reactions was 3/3 (100%) compared to 3/8 (38%) in patients with normal renal function. Additionally, the AUC of MMAE (component of ADCETRIS) was approximately 2-fold higher 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.

8.7 Hepatic Impairment

Avoid the use of ADCETRIS in patients with moderate or severe hepatic impairment.

The liver is a route of clearance for MMAE. The pharmacokinetics and safety of brentuximab vedotin and MMAE were evaluated after the administration of 1.2 mg/kg of ADCETRIS to patients with mild (Child-Pugh A; n=1), moderate (Child-Pugh B; n=5) and severe (Child-Pugh C; n=1) hepatic impairment. In patients with moderate and severe hepatic impairment, the rate of \geq Grade 3 adverse reactions was 6/6 (100%) compared to 3/8 (38%) in patients with normal hepatic function. Additionally, the AUC of MMAE was approximately 2.2-fold higher in patients with hepatic impairment compared to patients with normal hepatic function.

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.

• 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.



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Baseline Metabolic Tumor Volume Is an Independent Prognostic Factor for Relapsed and Refractory Hodgkin Lymphoma Patients Receiving PET-Adapted Salvage Therapy With Brentuximab Vedotin and Augmented ICE

Current treatments for Hodgkin lymphoma (HL) yield excellent response rates, and many patients experience prolonged disease-free survival. However, treatments continue to cause long-term toxicities, underscoring the need for new treatment paradigms. For patients with relapsed or refractory HL, negative results from ^{18}F -fluorodeoxyglucose positron emission tomography (PET) imaging correlates with a positive outcome after high-dose chemotherapy and autologous stem cell transplant (SCT). At the 14th International Conference on Malignant Lymphoma (ICML), Dr Alison Moskowitz presented findings from a phase 2 study of PET-adapted salvage therapy with augmented ifosfamide, carboplatin, and

etoposide (ICE) plus brentuximab vedotin.¹ The study also evaluated clinical factors and serum markers as potential prognostic factors.

Eligible patients had relapsed or refractory HL after a single line of therapy and were eligible for transplant. Brentuximab vedotin (1.2 mg/kg) was administered on days 1, 8, and 15 in 28-day cycles. Patients in cohort 1 received 2 cycles of brentuximab vedotin, and patients in cohort 2 received 3 cycles. Patients with a negative PET scan following brentuximab vedotin proceeded to autologous SCT. Patients with a positive PET scan were treated with augmented ICE and then underwent autologous SCT. Augmented ICE consisted of 2 doses of ifosfamide (5000 mg/m²) in

combination with mesna (5000 mg/m²) given in a continuous infusion over 24 hours on days 1 and 2; a single dose of carboplatin (area under the curve, 5) on day 3; and 3 doses of etoposide (200 mg/m²) every 12 hours on day 1. Serum cytokines and chemokines were measured at baseline and after administration of brentuximab vedotin. They included interferon (γ), thymus and activation-regulated chemokine (TARC), interleukin 6, interleukin 10, and tumor necrosis factor α . Metabolic tumor volume and total lesion glycolysis were measured at baseline, after brentuximab vedotin therapy, and after augmented ICE therapy.

The study included 45 patients in cohort 1 and 20 patients in cohort 2. In the entire study population, 52% were female, 45% had advanced-stage disease, and 52% had not responded to first-line therapy. Fifteen percent of patients had B symptoms, 37% had extranodal disease, and 25% had bulky disease. After treatment with brentuximab vedotin, 28% of patients exhibited a complete response (CR), defined as a Deauville score of 2 or lower. All of these patients proceeded to autologous SCT. In addition, 1 patient with a Deauville score of 3 proceeded directly to autologous SCT. Among 45 patients who received augmented ICE therapy, 31 (69%) achieved a CR. In total, 64 patients proceeded to autologous SCT, and 1 patient was lost to follow-up.

Three-year overall survival was 95%, and 3-year event-free survival was 82% (Figure 1). In a univariate analysis, reduced event-free survival was associated with older age (>45 years; $P=.016$), refractory disease ($P=.033$), B symptoms ($P=.032$), and advanced disease stage at relapse

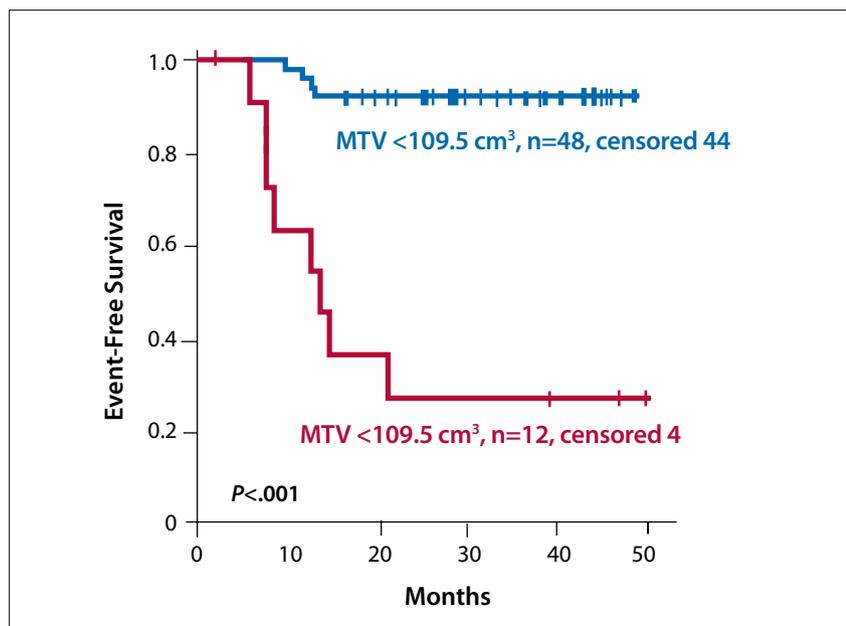


Figure 1. Event-free survival in a phase 2 study of PET-adapted salvage therapy with augmented ICE and brentuximab vedotin. ICE, ifosfamide, carboplatin, and etoposide; MTV, metabolic tumor volume; PET, positron-emission tomography. Adapted from Moskowitz AJ et al. ICML abstract 018. *Hematol Oncol.* 2017;35(suppl S2).¹

($P=.011$). Baseline levels of TARC, metabolic tumor volume, and total lesion glycolysis also correlated with event-free survival ($P<.001$ for each). In a multivariate analysis, metabolic tumor volume and refractory disease remained predictive of event-free

survival. Using an optimized cutoff value of 109.5 cm^3 for metabolic tumor volume, the 3-year event-free survival was 92% among 48 patients with low metabolic tumor volume and 27% in the 12 patients with high metabolic tumor volume.

Reference

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Copanlisib in Patients With Relapsed or Refractory Indolent B-Cell Lymphoma (CHRONOS-1)

The phosphoinositide 3-kinase cascade represents a key signaling pathway downstream of the B-cell receptor and affects B-cell growth, development, and survival. Copanlisib (BAY 80-6946) is an intravenous, pan-class I phosphoinositide 3-kinase inhibitor that has demonstrated strong binding activity against p110 α and p110 δ isoforms, with IC_{50} values of 0.5 nmol/L and 0.7 nmol/L, respectively.¹ In phase 1/2 trials conducted in patients with relapsed or refractory indolent lymphoma, copanlisib demonstrated clinical activity and an acceptable safety profile. At the ICML, Dr Martin Dreyling presented results from the phase 2 CHRONOS-1 study (Open-Label, Uncontrolled Phase II Trial of Intravenous PI3K Inhibitor BAY80-6946 in Patients With Relapsed, Indolent or Aggressive Non-Hodgkin's Lymphomas), which evaluated copanlisib in patients with relapsed or refractory indolent lymphoma.² Eligible patients had indolent B-cell non-Hodgkin lymphoma (NHL), including follicular lymphoma, marginal zone lymphoma, small lymphocytic leukemia, and lymphoplasmacytoid/Waldenström macroglobulinemia. All patients had received at least 2 previous lines of treatment, which included rituximab and an alkylating agent. Copanlisib (60 mg) was administered intravenously on days 1, 8, and 15 of a 28-day cycle. The primary efficacy endpoint

was the objective response rate (ORR) by independent radiologic review.³

The full analysis set of 142 patients included 104 with follicular lymphoma and 23 with marginal zone lymphoma. The 142 patients had a median age of 63 years. The median time since their most recent disease progression was 8.3 months, and they had received a median of 3 prior regimens. Stage III/IV disease was present in 80.3% of patients at baseline. The

median duration of treatment was 22 weeks (range, 1-105 weeks), and 46 patients remained on treatment. Patients received a median 5.5 cycles of therapy.

The ORR was 59.2%, including a CR rate of 12.0% and a partial response (PR) rate of 47.2% (Table 1). Stable disease was observed in 29.6% of patients. In patients with follicular lymphoma, the ORR was 58.7%, including a CR rate of 14.4%. In

ABSTRACT SUMMARY Interim Report From a Phase 2 Multicenter Study of Tazemetostat, an EZH2 Inhibitor, in Patients With Relapsed or Refractory B-Cell Non-Hodgkin Lymphomas

Tazemetostat is a selective inhibitor of EZH2, a histone methyltransferase that plays a key role in regulating transcription and is implicated in the development of DLBCL and follicular lymphoma. An open-label, multicenter phase 2 study evaluated the safety and efficacy of oral tazemetostat (800 mg twice daily) in patients with previously treated DLBCL or follicular lymphoma (ICML Abstract 004). The DLBCL cohort included 17 patients with mutated *EZH2* and 119 with wild-type *EZH2*. The follicular lymphoma cohort included 13 patients with mutated *EZH2* and 54 with wild-type *EZH2*. The median number of prior lines of therapy was 3 for patients with DLBCL and 4 for patients with follicular lymphoma. Among 203 evaluable patients, the ORR was 92% in follicular lymphoma patients with mutated *EZH2*, 26% in follicular lymphoma patients with wild-type *EZH2*, 29% in DLBCL patients with mutated *EZH2*, and 15% in DLBCL patients with wild-type *EZH2*. In follicular lymphoma patients, the CR rate was 8% for mutated *EZH2* and 6% for wild-type *EZH2*. Among patients with DLBCL, the CR rate was 0% for those with mutated *EZH2* and 8% for those with wild-type *EZH2*. No progressive disease was observed in any follicular lymphoma or DLBCL patient with mutated *EZH2*. A treatment-related AE of grade 3 or higher occurred in 59% of patients, and 10% of patients experienced a serious treatment-related AE. Treatment-related AEs led to a dose reduction in 15% of patients.

Table 1. Outcome With Copanlisib in the CHRONOS-1 Trial

	Follicular Lym- phoma (n=104)	Marginal Zone Lymphoma (n=23)	Small Lymphocytic Leukemia (n=8)	LPL/WM (n=6)	Total (N=142)
Best response, n (%)					
Complete response	15 (14.4)	2 (8.7)	0	0	17 (12)
Partial response	46 (44.2)	14 (60.9)	6 (75.0)	1 (16.7)	67 (47.2)
Stable disease	35 (33.7)	4 (17.4)	1 (12.5)	3 (50.0)	42 (29.6)
Progressive disease	2 (1.9)	0	1 (12.5)	0	3 (2.1)
NE/NA	6 (5.8)	3 (13.0)	0	2 (33.3)	12 (8.5)
ORR, n (%)	61 (58.7)	16 (69.6)	6 (75)	1 (16.7)	84 (59.2)
95% CI	48.6-68.2	47.1-86.6	34.9-96.8	0.4-64.1	50.6-67.3
Disease control rate, n (%)	91 (87.5)	20 (87.0)	7 (87.5)	4 (66.7)	122 (85.9)
95% CI	79.6-93.2	66.4-97.2	47.4-99.7	2.3-95.7	79.1-91.2

CHRONOS-1, Open-Label, Uncontrolled Phase II Trial of Intravenous PI3K Inhibitor BAY80-6946 in Patients With Relapsed, Indolent or Aggressive Non-Hodgkin's Lymphomas; LPL, lymphoplasmacytoid; NA, not available; NE, not evaluable; WM, Waldenström macroglobulinemia.

Adapted from Dreyling M et al. *Hematol Oncol.* 2017;35(suppl S2).²

patients with marginal zone lymphoma, the ORR was 69.6%, with a CR rate of 8.7%. Based on Kaplan-Meier analysis, the estimated median duration of response was 687 days in the entire study population, but decreased to 370 days in patients with follicular lymphoma. The estimated

median progression-free survival (PFS) was 340 days (range, 0-736 days). In 91% of evaluable patients, the best response was tumor shrinkage.

The most common treatment-related adverse events (AEs) of any grade were transient hyperglycemia (49%), hypertension (29%), and neu-

tropenia (25%). The most common treatment-related AEs of grade 3 or higher were also hyperglycemia (40%), hypertension (23%), and neutropenia (19%). Two nonfatal opportunistic infections were reported. Among the 6 patients who died, the cause of death was attributed to copanlisib in 3 cases (from lung infection, respiratory failure, and a thromboembolic event). Laboratory toxicities of interest included elevated alanine transaminase (occurring in 23%, mostly grade 1) and elevated aspartate transaminase (occurring in 28%, mostly grade 1). Copanlisib is being evaluated in phase 3 studies in patients with relapsed or refractory indolent NHL.

ABSTRACT SUMMARY Risk-Adapted Therapy Utilizing Upfront Brentuximab Vedotin and Rituximab With Reduced Toxicity Chemotherapy in Children, Adolescents, and Young Adults With Hodgkin Lymphoma

The addition of brentuximab vedotin and rituximab to chemotherapy was evaluated in a phase 2 trial of young patients with newly diagnosed HL (ASCO Abstract 10532). Patients with low-risk disease received brentuximab vedotin plus doxorubicin, vincristine, prednisone, and dacarbazine, and patients with intermediate-risk or high-risk disease received the same regimen plus rituximab. Early response was assessed by a PET/CT scan after 2 treatment cycles. Further risk-adapted therapies included additional cycles of immunochemotherapy for intermediate-risk patients, ifosfamide/vinorelbine for high-risk patients, and radiation therapy for patients who did not respond completely. Twenty patients completed therapy. Their median age was 15 years (range, 4-23 years). Three patients had low-risk disease, 13 had intermediate-risk, and 4 had high-risk. Eleven patients had B symptoms, and 4 had bulky disease. The ORR was 100%. Approximately half of patients had an early response, including all 3 patients with low-risk disease. One patient received radiation therapy. At a median follow-up of 34 months, the probability of event-free survival and overall survival in the 22 patients evaluable for early response was 100%. AEs of grade 3 or higher included 1 case each of mucositis, neuropathy, and infusion reaction related to brentuximab vedotin (all grade 3).

References

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2. Dreyling M, Santoro A, Mollica L, et al. Copanlisib in patients with relapsed or refractory indolent B-cell lymphoma (CHRONOS-1) [ICML abstract 108]. *Hematol Oncol.* 2017;35(suppl S2).
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Brentuximab Vedotin in Combination With Nivolumab in Patients With Relapsed or Refractory Hodgkin Lymphoma

CD30 is a marker of the malignant Reed-Sternberg cells that characterize classical HL, and it is rarely expressed by normal cells.¹ Brentuximab vedotin is an antibody-drug conjugate that targets CD30 and is conjugated to the microtubule-disrupting agent monomethyl auristatin E by a protease-cleavable linker. Binding to CD30 leads to internalization of the conjugate and endocytosis into a lysosome, where proteases release the monomethyl auristatin E. Subsequent binding of monomethyl auristatin E to tubulin induces cell cycle arrest and apoptosis. Nivolumab is a monoclonal antibody that binds to programmed death protein 1, a negative regulator of T-cell activation. By binding to this protein, nivolumab blocks the immune checkpoint pathway, thus preventing T-cell inactivation. Both brentuximab vedotin and nivolumab have demonstrated single-agent activity in patients

with relapsed or refractory HL. By using the 2 drugs in combination, it may be possible to simultaneously provoke tumor cell killing and antigen release with brentuximab vedotin while inducing antitumor immune activation with nivolumab.

The combination of brentuximab vedotin and nivolumab was investigated in 2 trials of patients with relapsed or refractory HL. Dr Catherine Diefenbach presented preliminary results from 2 arms of the phase 1 E4412 trial at the ICML.² This dose escalation and expansion trial used a 3-plus-3 design and an expansion cohort of 9 patients. Study participants received nivolumab (3 mg/kg) plus brentuximab vedotin (1.2 mg/kg in arm D and 1.8 mg/kg in arm E). The 2 drugs were administered together every 21 days for 16 cycles, and nivolumab could be continued for an additional year. Nineteen patients with confirmed relapsed or refractory

HL were enrolled. Patients had a median age of 40 years (range, 21-70 years), and 9 patients (45%) were male. Patients had received a median of 3 prior therapies. Eight patients had received prior SCT, and 4 had received prior brentuximab vedotin.

Among 18 patients evaluable for response, the ORR was 89%, including a CR rate of 50% (95% CI, 26%-74%; Figure 2). The results included 2 CRs and 1 PR in patients who had received prior treatment with brentuximab vedotin. The 6-month PFS was 91% (95% CI, 75%-100%). The median overall survival was not reached, at a median follow-up of 6 months.

Grade 3 AEs included 1 event each of rash, pruritus, and neutropenia. The most common grade 1/2 AEs included transaminitis (n=9), peripheral sensory neuropathy (n=8), and rash (n=6). One patient experienced a grade 1/2 infusion reaction but was able to receive subsequent therapy after premedication. Two notable treatment-related AEs occurred among the 19 patients in the safety population. One patient in arm E experienced a dose-limiting toxicity characterized by grade 3 pneumonitis and grade 3 dyspnea, along with hypoxia and neutropenic enterocolitis. This patient fully recovered. One patient in the expansion cohort (arm F) developed grade 5 pneumonitis during cycle 2.

At the ICML, Dr Alex Herrera presented preliminary findings from a phase 1/2 study that examined brentuximab vedotin plus nivolumab in patients with relapsed or refractory HL.³ Enrolled patients had progressive disease after first-line treatment. Study treatment was administered in 21-day cycles for a maximum of 4 cycles. In cycle 1, patients received brentuximab vedotin on day 1 and nivolumab

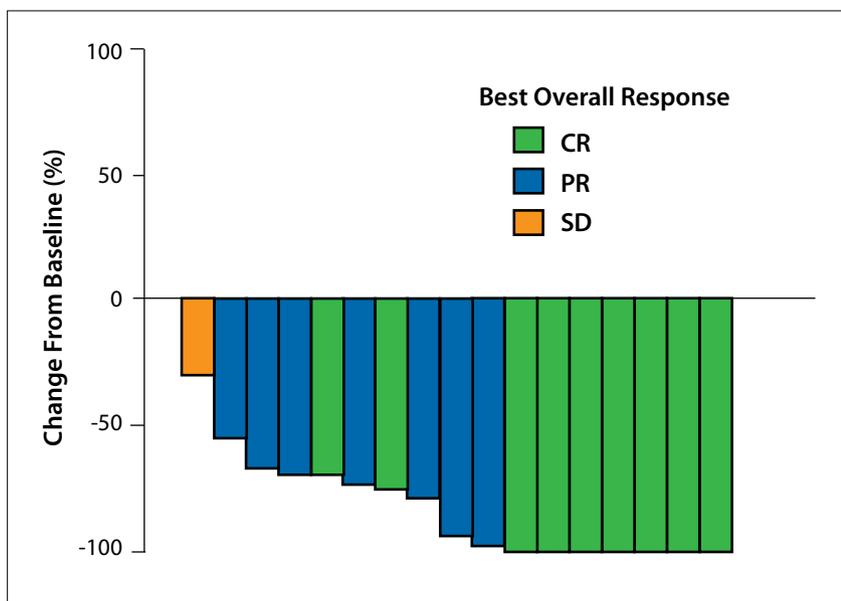


Figure 2. Best overall response in a study of nivolumab plus brentuximab vedotin. CR, complete response; PR, partial response; SD, stable disease. Adapted from Diefenbach CS et al. ICML abstract 073. *Hematol Oncol.* 2017;35(suppl S2).²

ABSTRACT SUMMARY A Phase I Trial of 19-28X CAR-T Cells Post-High Dose Therapy and Autologous Transplantation for Relapsed and Refractory B-Cell Non-Hodgkin Lymphoma

A phase 1 trial evaluated treatment with 19-28z CAR T cells after treatment with high-dose therapy and autologous SCT in patients with relapsed or refractory, poor-risk, aggressive B-cell NHL (ICML Abstract 129). Enrolled patients had relapsed or refractory B-cell NHL with bone marrow involvement or a positive fluorodeoxyglucose PET scan after 2 cycles of salvage therapy. The patients' T cells were engineered to express an anti-CD19 single-chain Fv domain linked to the CD28 and CD3 ζ signaling domains. Patients underwent conditioning with carmustine, etoposide, cytarabine, and melphalan, followed by autologous SCT, with 19-28z CAR T cells administered on days +2 and +3. Fifteen patients were treated. Their median age was 61 years (range, 34-75 years). Fourteen patients were treated at dose level 1 (5×10^6 19-28z CAR T cells/kg) and 1 was treated at dose level 2 (1×10^6 CAR T cells/kg). One dose-limiting toxicity was observed at each dose level. Ten of 15 patients (67%) experienced grade 2 to 4 neuropathy or cytokine release syndrome; all cases were reversible. 19-28z CAR T cells persisted for a longer time in patients with toxicity events compared with patients who did not experience toxicity events (median of 11 days vs 4 days; $P=.05$). IFN- γ was upregulated and associated with toxicity following CAR T-cell infusion ($P<.001$), with a similar trend observed for interleukin 10 ($P=.07$). After a median follow-up of 31 months for survivors, PFS was 30% (95% CI, 20%-70%).

on day 8. For cycles 2 to 4, patients received both drugs on day 1 of each cycle. After an assessment following cycle 4, patients could undergo autologous SCT. Responses were assessed based on the Lugano classification.⁴

The 62 enrolled patients had a median age of 36 years, and 52% were female. Forty-five percent had primary refractory HL. Among 61 patients who received combination treatment, 53 completed 4 cycles of treatment, 5 remained on treatment, and 4 discontinued (based on decisions by the patient [$n=2$] or the investigator [$n=1$], and owing to an AE [$n=1$]).

Among 55 patients in the efficacy population, the ORR was 84% and included a CR rate of 64%. Four patients (7%) had stable disease, and 3 patients (5%) progressed on treatment. Twenty-nine patients initiated

autologous SCT. A median of 4.7×10^6 CD34-positive cells/kg were collected. The median time to engraftment was 11.5 days for neutrophils and 16 days for platelets. Effects on the immune system were evaluated by peripheral blood analysis and included a decrease in CD30-positive T-regulatory cells after administration of brentuximab vedotin in cycle 1, with levels of CD8-positive T lymphocytes remaining stable. After treatment with the 2-drug combination, levels of CD4-positive T cells increased, and T-cell receptor sequencing demonstrated clonal expansion. Serum levels of TARC decreased with brentuximab vedotin alone and were accompanied by increased levels of IFN- γ and CXCL10.

Infusion-related reactions were observed in 41% of patients; they occurred most frequently during

infusion of brentuximab vedotin in cycle 2. Twenty-five percent of patients required dose interruptions. Grade 3 infusion-related reactions occurred in less than 5% of patients. Sixty patients (98%) developed treatment-emergent AEs prior to autologous SCT; these events were grade 3 in 28% and grade 4 in 5%. The most common treatment-emergent AEs were nausea (49%) and fatigue (33%), both grade 1. Outside of infusion-related reactions, potential immune-related AEs occurred in 72% of patients, including grade 3/4 events in 7%. Grade 1 diarrhea occurred in 25% of patients. Systemic corticosteroids were required in 4 patients, for treatment of grade 4 pneumonitis and colitis, grade 3 aspartate transferase elevation, grade 3 diarrhea and grade 2 colitis, and grade 2 pneumonitis.

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CR Rates in Relapsed/Refractory Aggressive B-NHL Treated With the CD19-Directed CAR T-Cell Product JCAR017 (TRANSCEND NHL 001)

JCAR017 is a CD19-directed chimeric antigen receptor (CAR) T-cell product with a 4-1BB costimulatory domain and a defined combination of CD4-positive and CD8-positive T cells. At the 2017 American Society of Clinical Oncology (ASCO) meeting, Dr Jeremy Abramson presented findings from the phase 1 TRANSCEND NHL 001 trial (Study Evaluating the Safety and Pharmacokinetics of JCAR017 in B-Cell Non-Hodgkin Lymphoma [NHL]), a multicenter dose-finding study that evaluated lymphodepletion with fludarabine and cyclophosphamide followed by JCAR017 in patients with relapsed or refractory aggressive NHL.¹ In addition to enrolling hard-to-treat patients, such as those with

central nervous system involvement, the trial included patients with diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma, grade 3B follicular lymphoma, and mantle cell lymphoma. The regimen for lymphodepletion therapy consisted of fludarabine (30 mg/m²) and cyclophosphamide (300 mg/m²), administered for 3 days. Patients received JCAR017 cells at 3 dose levels: dose level 1, 5×10^7 cells; dose level 2, 1×10^8 cells; and dose level 3, 1.5×10^8 cells. Although the original protocol included 1 or 2 T-cell treatments, the 2-dose schedule was suspended. After the final dose of JCAR017, patients transitioned to long-term follow-up, which will last up to 15 years.

The core group of patients con-

sisted of those with relapsed/refractory DLBCL and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. This core group of patients will be enrolled in the upcoming pivotal trial of JCAR017. Patients in the full analysis cohort are those with an ECOG performance status of 2 or who have rare subtypes of DLBCL.

The T-cell product was available for 98% of the patients (86/88) who underwent apheresis, and the product met study specifications in 89% (78/88). In the core group, the ORR was 86% (38/44), with a CR rate of 59% (26/44). The 3-month ORR was 66% (21/32), with a CR rate of 50% (16/32). Among patients who had a response lasting 3 months and had follow-up data for at least 6 months, 90% (9/10) remained in response. In patients treated at the lowest dose level, the ORR was 58% (11/19), and the CR rate was 42% (8/19). In patients treated at dose level 2, the ORR was 78% (7/9), with a CR rate of 56% (5/9). These early data suggested a potential dose response.

As of the data cutoff on May 4, 2017, 97% of patients (37/38) who responded were alive and in follow-up (Figure 3). In the core group, severe cytokine release syndrome occurred in 2% (1/44) of patients, and 8 patients (18%) experienced severe neurotoxicity. Two-thirds of patients did not experience any cytokine release syndrome or neurotoxicity. One 82-year-old patient died on day 23 from diffuse alveolar damage that was considered related to lymphodepletion and engineered T-cell treatments. The patient was treated with antibiotic and antifungal agents as well as growth factors, after refusing mechanical ventilation.

For the full analysis set of 54

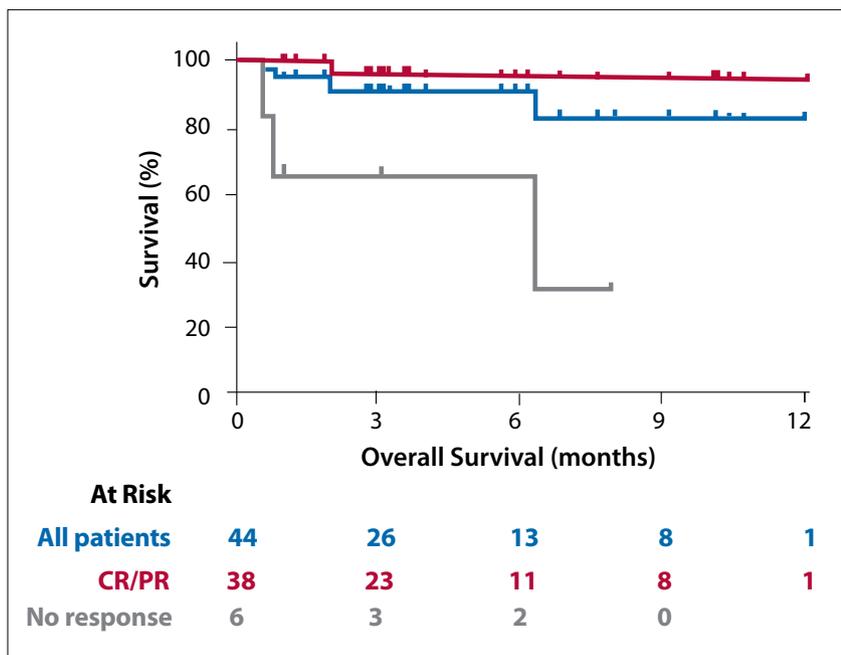


Figure 3. Response in the core group of patients with DLBCL treated in the TRANSCEND NHL 001 trial. CR, complete response; DLBCL, diffuse large B-cell lymphoma; PR, partial response; TRANSCEND NHL 001, Study Evaluating the Safety and Pharmacokinetics of JCAR017 in B-Cell Non-Hodgkin Lymphoma (NHL). Adapted from Abramson JS et al. ASCO abstract 7513. *J Clin Oncol.* 2017;35(15 suppl).¹

patients treated across all dose levels, the ORR was 76% (41/54), and the CR rate was 52% (28/54). The 3-month ORR was 51% (21/41), with a 3-month CR rate of 39% (16/41).

Among 55 patients in the safety population, the most common treatment-emergent AEs were neutropenia (35%), cytokine release syndrome (35%), and fatigue (31%). However, most patients (60%) did not experience cytokine release syndrome or neurotoxicity. There was 1 case of

severe cytokine release syndrome, and 9 patients experienced severe neurotoxicity. No deaths occurred from cytokine release syndrome or neurotoxicity, and there was no relationship between dose and toxicity. Cytokine release syndrome occurred in 3% of patients (1/30) treated at dose level 1, but no cases were observed in the 19 patients treated at dose level 2. The severe neurotoxicity rate was 20% (6/30) at dose level 1 and 11% (2/19) at dose level 2. To manage these

toxicities, 11% of patients (6/55) received tocilizumab and 24% (13/55) received dexamethasone. Enrollment of the TRANSCEND NHL 001 pivotal cohort will begin in late 2017. The trial will evaluate treatment with an optimized JCAR017 T-cell product.

Reference

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Outcomes by CD30 Expression in Patients With CTCL Receiving Brentuximab Vedotin Vs Physician's Choice in the Phase 3 ALCANZA Study

CD30 expression is generally high in primary cutaneous anaplastic large cell lymphoma (pcALCL), with at least three-fourths of cells typically expressing the marker.¹ However, the cells of mycosis fungoides show variable levels of CD30 expression, and CD30 is only rarely expressed in the cells of some patients.^{2,3} The phase 3 ALCANZA study (A Phase 3 Trial of Brentuximab Vedotin [SGN-35] Versus Physician's Choice [Methotrexate or Bexarotene] in Patients With CD30-Positive Cutaneous T-Cell Lymphoma) evaluated brentuximab vedotin vs physician's choice of methotrexate or bexarotene in previously treated patients with CD30-positive mycosis fungoides or pcALCL.⁴ The patients with mycosis fungoides had 2 or more skin biopsies from separate skin lesions obtained at screening, and patients with pcALCL had at least 1 skin biopsy. Biopsies with at least 10% CD30-positive lymphoid cells compared with a negative control were considered CD30-positive.

This open-label, international, multicenter study randomly assigned 66 patients to brentuximab vedotin vs

65 to the physician's choice of methotrexate or bexarotene. Rates of ORR lasting at least 4 months (ORR4) were 56% with brentuximab vedotin

vs 13% in the control arm ($P < .0001$). The CR rate was 16% vs 2%, respectively (adjusted $P = .0046$). PFS was superior with brentuximab vedotin, at

ABSTRACT SUMMARY Phase 2 Trial of Brentuximab Vedotin and Gemcitabine for Pediatric and Young Adult Patients With Relapsed or Refractory Lymphoma: A Children's Oncology Group Report

The phase 2 trial AHOD1221 evaluated brentuximab vedotin plus gemcitabine in children and young adults with HL (ASCO Abstract 7527). Eligible patients had primary refractory HL or advanced-stage HL with early relapse. The primary objective was the CR rate within 4 treatment cycles. Patients received brentuximab vedotin (1.8 mg/kg) on day 1 and gemcitabine (1000 mg/m²) on days 1 and 8 in 21-day cycles. Among the 42 treated patients, the median age was 17.4 years (range, 5.4-28.7 years). Two patients with stable disease were removed from the study after 2 treatment cycles and were unevaluable for response. The median duration of therapy was 4 cycles. Two patients had received more than 14 cycles and were still being treated at the time of the report. The ORR for 40 evaluable patients was 73% (95% CI, 59%-86%). Twenty-three patients (58%) achieved a CR within 4 treatment cycles, and the majority of CRs occurred within 2 treatment cycles. Thirty-three patients underwent autologous and/or allogeneic SCT. The 1-year overall survival was 94% (95% CI, 77%-99%) among enrolled patients and 100% among the 40 patients evaluable for response. Grade 4 hematologic toxicities in cycle 1 included neutropenia (33%), thrombocytopenia (7%), and anemia (2%). Nonhematologic toxicities of grade 3 or higher in cycle 1 included maculopapular rash (36%), elevated alanine transaminase (21%), elevated aspartate transaminase (17%), and pruritus (10%).

16.7 months vs 3.5 months (adjusted $P < .0001$). Brentuximab vedotin also reduced symptoms (-27.96 vs -8.62 ; adjusted $P < .0001$).

Dr Youn Kim and colleagues analyzed the subgroup of patients with mycosis fungoides in the ALCANZA study.⁵ Results were presented at the ASCO meeting and the ICML. The analysis compared response among patients with at least 10% CD30-positive cells in all biopsies vs those with at least 1 biopsy that showed less than 10% CD30-positive cells. At screening, 68% of mycosis fungoides patients (125/184) and 94% of the pcALCL patients (44/47) were CD30-positive. Biopsies from mycosis fungoides patients showed high interlesional variability, and 44% of these patients (55/125) had at least 1 biopsy with low or undetectable CD30. Fifty patients with mycosis fungoides were enrolled into each treatment arm.

ORR4 was higher in mycosis

fungoides patients with CD30 expression in at least 10% of biopsy cells compared with patients showing CD30 expression in less than 10% of cells (57.1% vs 40.9%). Terciles for CD30 expression were established, and the ORR4 was superior with brentuximab vedotin vs physician's choice across all ranges. Median PFS was superior with brentuximab vedotin vs physician's choice in mycosis fungoides patients with less than 10% CD30-positive cells (27.9 months vs 2.3 months; hazard ratio [HR], 0.125; 95% CI, 0.044-0.355) and in those with at least 10% CD30-positive cells (17.2 months vs 3.5 months; HR, 0.176; 95% CI, 0.072-0.432). Approximately one-third of mycosis fungoides patients were excluded from the trial based on low CD30 expression. However, 9 of 22 enrolled patients with mycosis fungoides who achieved ORR4 had at least 1 biopsy with fewer than 10% CD30-positive cells, suggesting that

some patients with low CD30 expression may benefit from treatment with brentuximab vedotin. Baseline CD30 expression levels did not correlate with toxicity.

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Bendamustine Plus Rituximab Versus CHOP Plus Rituximab as First-Line Treatment in Patients With Indolent Lymphomas: Nine-Year Updated Results From the StiL NHL1 Study

Bendamustine plus rituximab was compared with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in the phase 3 NHL1 trial of treatment-naïve patients with indolent lymphoma or mantle cell lymphoma.¹ This open-label, multicenter, investigator-initiated, noninferiority trial was conducted by the Studiengruppe Indolente Lymphome. The study enrolled patients between September 2003 and August 2008, and 420 were eligible for response. Eligible patients were adults with newly diagnosed stage III/IV indolent lymphoma or mantle cell lymphoma and a World Health Organization performance status of 0 to 2. After

stratification by lymphoma subtype, patients were randomly assigned to receive a maximum of 6 cycles of either bendamustine (90 mg/m²) on days 1 and 2 in 28-day cycles; or cyclophosphamide (750 mg/m²), doxorubicin (50 mg/m²), and vincristine (1.4 mg/m²) on day 1, plus prednisone (100 mg daily) for 5 days in 21-day cycles. All patients also received rituximab (375 mg/m²) on day 1 of each cycle. PFS was the primary endpoint, with a noninferiority margin of 10%.

As Dr Mathias Rummel reported at the ASCO meeting, the initial analysis included 215 patients in the bendamustine/rituximab arm and 205 in the R-CHOP arm.² Patients had a median age of 62 years. Three-fourths

of patients had stage IV disease, and 64% had bone marrow involvement. B symptoms were present in 29% to 37% of patients in each arm, and bulky disease was present in 30% to 33%.

After a median follow-up of 45 months, median PFS was 69.5 months for patients treated with bendamustine/rituximab vs 31.2 months in the R-CHOP arm (HR, 0.58; 95% CI, 0.44-0.74; $P = .0000148$). Bendamustine/rituximab improved PFS in patients with follicular lymphoma ($P = .0072$), mantle cell lymphoma ($P = .0061$), and Waldenström macroglobulinemia ($P = .0033$). The time to next treatment was not reached for bendamustine/rituximab vs 42.3

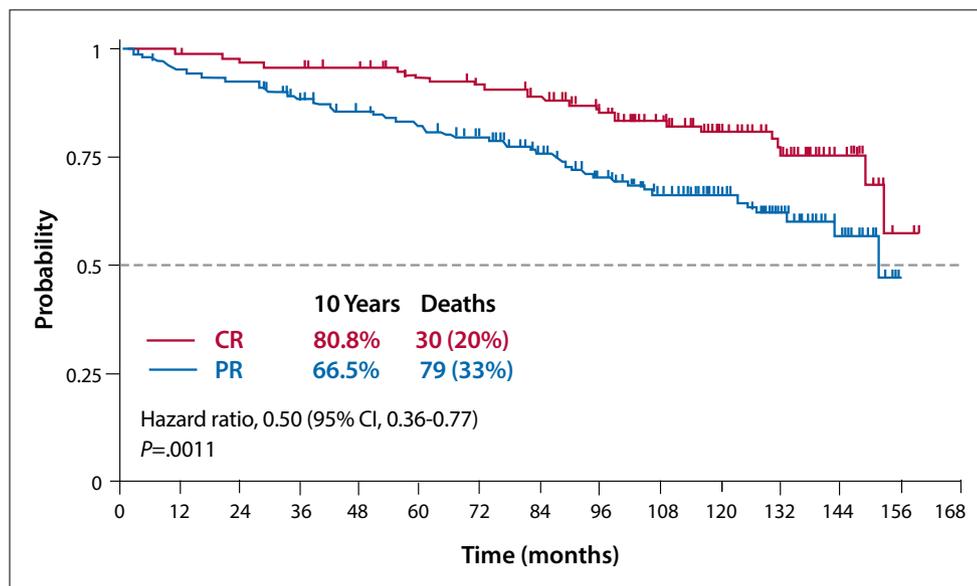


Figure 4. In the StiL NHL1 trial of bendamustine plus rituximab vs R-CHOP, patients who achieved a CR had better 10-year overall survival than those who achieved a PR. CR, complete response; PR, partial response; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; StiL, the Studiengruppe Indolente Lymphome. Adapted from Rummel M et al. ASCO abstract 7501. *J Clin Oncol*. 2017;35(15 suppl).²

months for R-CHOP (HR, 0.52; 95% CI, 0.39-0.69; $P < .0001$). Although erythematous skin reactions were more common with bendamustine/rituximab, the 2-drug combination showed better tolerability than R-CHOP in rates of alopecia ($P < .0001$), hematologic toxicity ($P < .0001$), infections ($P = .0025$), peripheral neuropathy ($P < .0001$), and stomatitis ($P < .0001$).

At the ASCO meeting, Dr Rummel presented updated results from the trial, after a median follow-up of 117 months.² Main objectives for the follow-up analysis included overall survival, time to next treatment, and secondary malignancies, with additional endpoints of salvage regimens administered after cessation of study treatment and causes of death. The updated analysis showed a significant benefit in median time to next treatment for bendamustine/rituximab compared with R-CHOP (not reached vs 56.0 months; HR, 0.55; 95% CI, 0.41-0.73; $P < .0001$). Patients in the bendamustine/rituximab arm required fewer second-line treatments for disease progression (36% vs 53%). In the bendamustine/rituximab arm, the most common second-line salvage regimen was R-CHOP (administered to 27 patients, vs 2 in the R-CHOP arm). In the R-CHOP arm, the most common second-line salvage regimen

was bendamustine/rituximab (administered to 52 patients, vs 2 in the bendamustine/rituximab arm).

Survival was similar for patients in both arms, with a 10-year overall survival of 70.3% for bendamustine/rituximab and 66.3% for R-CHOP (HR, 0.82; 99% CI, 0.59-1.16; $P = .2665$). The 10-year overall survival was superior for patients who achieved a CR vs a PR (80.8% vs 66.5%; HR, 0.50; 95% CI, 0.36-0.77; $P = .0011$; Figure 4). Among the subset of patients who achieved a CR or PR (91.9%), overall survival was similar in both treatment arms (HR, 0.81; 95% CI, 0.55-1.17; $P = .2630$). Of the 133 deaths that occurred during the trial, 86 were caused by relapsed lymphoma.

Most patients in the study (63%) had normal levels of lactate dehydrogenase (LDH), and these patients had a superior median overall survival compared with patients whose LDH levels were low (not reached vs 127 months; HR, 0.45; 95% CI, 0.29-0.61; $P < .001$). In patients with normal levels of LDH, 10-year overall survival was superior with bendamustine/rituximab vs R-CHOP (80.0% vs 72.2%; HR, 0.61; 95% CI, 0.37-1.00; $P = .0499$). In patients with elevated LDH, however, both treatments had a similar overall survival at 10 years (HR,

1.01; 95% CI, 0.63-1.63; $P = .9576$). Among the 279 patients with follicular lymphoma, 54.5% had a Follicular Lymphoma International Prognostic Index (FLIPI) score of 0 to 2, and the remainder had a score of 3 to 5. Ten-year overall survival was 83.8% in patients with low FLIPI scores vs 58.0% in those with high scores (HR, 0.33; 95% CI, 0.22-0.54; $P < .0001$).

Secondary malignancies occurred in 37 patients (17%) in the bendamustine/rituximab arm (for a total of 39 events) and 40 patients (20%) in the R-CHOP arm (for a total of 47 events). These malignancies arose in the prostate, colon or stomach, bronchi, kidney or urothelium, breast, and other areas. Two patients in each arm developed myelodysplastic syndrome, and 1 patient in the R-CHOP arm developed acute myeloid leukemia.

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Results of a Phase II Study of Brentuximab Vedotin in the First-Line Treatment of Hodgkin Lymphoma Patients Considered Unsuitable for Standard Chemotherapy (BREVITY)

At the ICML, Dr Adam Gibb presented results of the phase 2 BREVITY trial (A Study of Brentuximab Vedotin in Patients With Hodgkin Lymphoma Unsuitable for Chemotherapy Due to Age, Frailty or Co-Morbidity), which evaluated the efficacy and tolerability of brentuximab vedotin in treatment-naïve HL patients who were unfit for standard treatment based on age, frailty, or comorbidities.¹ The single-arm trial had a response-adaptive, Simon 2-stage design and required 30 evaluable patients. The

primary outcome was complete metabolic response by centrally reviewed PET-computed tomography (CT) after 4 cycles of brentuximab vedotin monotherapy. The study enrolled several types of treatment-naïve patients: those with HL of stage 2 with B symptoms and/or mediastinal bulk (any age); those with stage 2, 3, or 4 disease with cardiorespiratory compromise (any age); and those ages 60 years or older with an ECOG performance status of 3 or higher who were considered unfit for standard chemotherapy. Brentuximab vedotin was

administered once every 3 weeks at a dose of 1.8 mg/kg. If patients developed toxicity, the dose was reduced to 1.2 mg/kg. Patients who exhibited a response after 4 doses of brentuximab vedotin continued to receive up to 16 cycles, for as long as an ongoing response was confirmed by PET/CT imaging every 4 weeks. Exploratory, blinded PET/CT was performed after cycle 2.

From February 2014 to October 2015, 38 patients were recruited at 12 centers in the United Kingdom. Patients had a median age of 76 years

Table 2. Patient Characteristics in the BREVITY Trial

Patient Characteristic (N=38)	n (%)
Sex	
Male	22 (57.9)
Female	16 (42.1)
Stage	
2	7 (18.4)
3	13 (34.2)
4	18 (47.4)
B symptoms	27 (71.1)
Bulky disease	5 (13.2)
Extranodal disease	22 (57.9)
ECOG performance status	
0	3 (7.9)
1	16 (42.1)
2	11 (28.9)
3	7 (18.4)
4	1 (2.6)

BREVITY, A Study of Brentuximab Vedotin in Patients With Hodgkin Lymphoma Unsuitable for Chemotherapy Due to Age, Frailty or Co-Morbidity; ECOG, Eastern Cooperative Oncology Group.

Adapted from Gibb A et al. ICML abstract 069. *Hematol Oncol.* 2017;35(suppl S2).¹

ABSTRACT SUMMARY Phase IIIb Randomized Study of Lenalidomide Plus Rituximab Followed by Maintenance in Relapsed/Refractory NHL: Analysis of Patients With Double-Refractory or Early Relapsed Follicular Lymphoma

The phase 3b MAGNIFY trial (Lenalidomide Plus Rituximab Followed by Lenalidomide Versus Rituximab Maintenance for Relapsed/Refractory Follicular, Marginal Zone or Mantle Cell Lymphoma) evaluated lenalidomide plus rituximab followed by maintenance therapy with the same combination or rituximab monotherapy in patients with relapsed or refractory follicular lymphoma, mantle cell lymphoma, or marginal zone lymphoma (ASCO Abstract 7502). Patients in the open-label, multicenter trial received 12 cycles of combination treatment, and those with stable disease or better were randomly assigned to each maintenance arm. Among 160 patients with follicular lymphoma, 52 patients had disease that relapsed within 2 years of the initial diagnosis (referred to as *early relapse*) and 50 had disease that was refractory to rituximab and an alkylating agent (referred to as *double-refractory*). Stage III/IV disease was present in 88% of patients in the double-refractory group and 83% in the early-relapse group. Among the patients who were evaluable for efficacy, the ORR was 66% (85/128) for all patients, 45% (19/42) in the double-refractory group, and 47% (20/43) in the early-relapse group. One-year PFS was 70% for all patients with follicular lymphoma (n=160), 65% for the double-refractory patients (n=50), and 49% for the early-relapse patients (n=52). With a median follow-up of 10.2 months for all patients, the median duration of response was not reached for double-refractory or early-relapse patients. The most common grade 3/4 treatment-emergent AEs were neutropenia (reported in 42% of the double-refractory group vs 37% of the early-relapse group), leukopenia (8% vs 10%), thrombocytopenia (8% vs 4%), and lymphopenia (6% vs 4%).

(range, 59-90 years), and 58% were male (Table 2). Eighty-one percent of patients had stage III/IV disease, 71% of patients had B symptoms, and 13% had bulky disease. Fifty-eight percent had extranodal involvement, and half had an ECOG performance status of 3 or greater. Thirty-five patients were evaluable for toxicity, and 31 were evaluable for response. Patients received a median of 4 cycles of treatment (range, 1-16 cycles).

The median PFS was 7.4 months (95% CI, 5.3-10.2 months). The rate of complete metabolic response after

4 treatment cycles was 26% (95% CI, 14%-43%), and the ORR was 84% (95% CI, 67%-93%). The complete metabolic response rate observed from PET/CT imaging after treatment cycle 2 was 32% (95% CI, 17%-52%). There was a significant correlation between interim PET/CT imaging results after cycle 2 and PET/CT imaging results after cycle 4 (Rho, 0.67; $P < .001$). Among 31 evaluable patients, 28 developed progressive disease.

Dose reductions owing to toxicity occurred in 14 patients throughout 28 cycles, and 11 patients stopped

treatment owing to an AE. Among 716 reported AEs, 626 (88%) were grade 1/2. The most common AEs of grade 3 or higher were infection, myelosuppression, and neuropathy, and 27 patients (77%) experienced at least 1 AE of grade 3 or higher.

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First-Line Treatment of iNHL or MCL Patients With BR or R-CHOP/R-CVP: Results of the BRIGHT 5-Year Follow-Up Study

The BRIGHT trial (Study of Bendamustine Hydrochloride and Rituximab [BR] Compared With R-CVP or R-CHOP in the First-Line Treatment of Patients With Advanced Indolent Non-Hodgkin's Lymphoma [NHL] or Mantle Cell Lymphoma [MCL]) evaluated the safety and efficacy of bendamustine/rituximab vs R-CHOP or rituximab plus cyclophosphamide, vincristine, and prednisone (R-CVP) as first-line treatment of indolent NHL or mantle cell lymphoma.¹ Eligible patients had CD20-positive, treatment-naive, indolent NHL, including grade 1 or 2 follicular lymphoma, lymphoplasmacytic lymphoma, splenic marginal zone B-cell lymphoma, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue type, nodal marginal zone B-cell lymphoma, or mantle cell lymphoma. All patients required treatment, as indicated by the presence of B symptoms, a large tumor mass, lymphoma-related complications, or hyperviscosity syndrome attributed to monoclonal gammopathy. The study excluded patients with chronic lymphocytic leukemia/small lymphocytic

lymphoma, grade 3 follicular lymphoma, or transformed disease.

In this open-label, noninferiority phase 3 trial, patients were randomly assigned to receive 6 cycles of bendamustine/rituximab in 21-day cycles vs R-CHOP or R-CVP in 28-day cycles, with 2 additional treatment cycles permitted based on the investigator's discretion. Supportive therapy was provided based on the standard of care of each treatment center. An independent review committee assessed responses. The primary objective was to determine whether the CR rate with bendamustine/rituximab was noninferior to that of standard immunochemotherapy, with a threshold CR rate of 88% of the rate obtained with standard therapy. The safety population included patients who had received at least 1 dose of the study drug. Patients were monitored yearly for at least 5 years, with a protocol amendment in 2012 for monitoring every 6 months.

The efficacy analysis included 213 patients in the bendamustine/rituximab arm and 206 in the standard treatment arm. The CR rate was noninferior with bendamustine/rituximab,

based on a CR rate of 31% with the 2-drug combination vs 25% with standard treatment (CR-rate ratio, 1.26; $P = .0225$ for noninferiority). The CR rate with bendamustine/rituximab was not statistically superior to standard immunochemotherapy ($P = .1269$).

The 2 treatment arms demonstrated different safety profiles. Patients treated with bendamustine/rituximab showed increased rates of any-grade drug hypersensitivity (17% vs 6%; $P < .05$), any-grade vomiting (29% vs 13%; $P < .01$), and grade 3/4 lymphopenia (61% vs 33%; $P < .0001$). Patients treated with R-CHOP or R-CVP had higher rates of any-grade peripheral neuropathy (44% vs 9%; $P < .0001$), any-grade alopecia (51% vs 4%; $P < .0001$), and grade 3/4 neutropenia (87% vs 39%; $P < .0001$). In addition to reductions in dyspnea, constipation, and fatigue associated with bendamustine/rituximab, quality of life was superior based on cognitive, physical, social, and emotional functioning, as well as global health status.²

Dr Ian Flinn presented results from 5-year follow-up of the BRIGHT

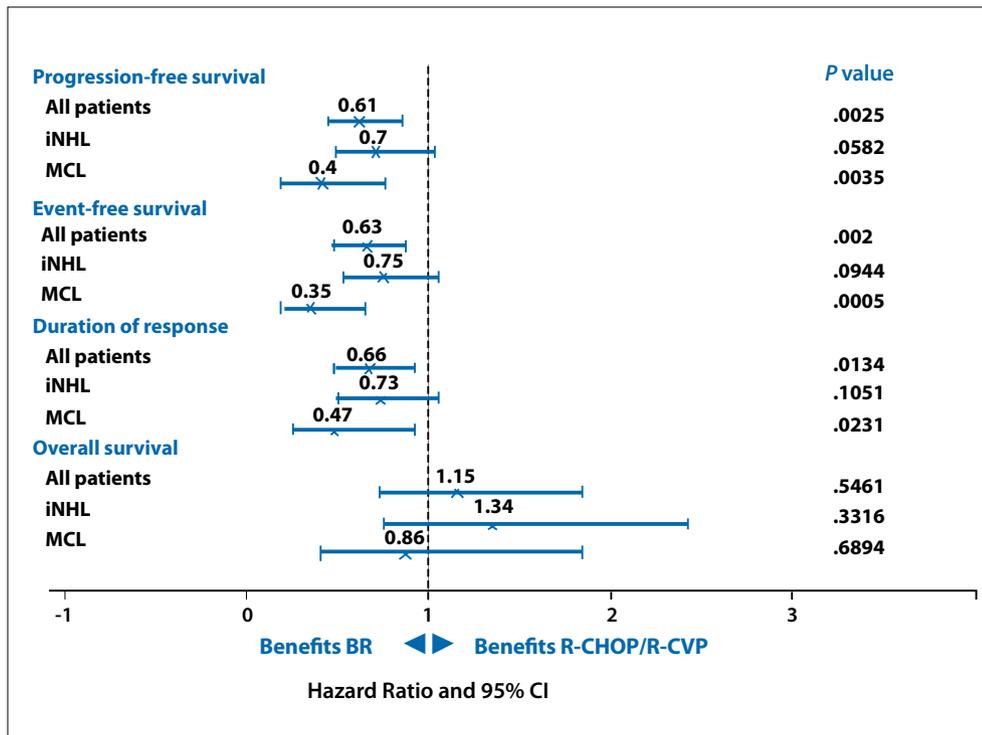


Figure 5. Time to events in a trial of BR vs immunochemotherapy. Data for the iNHL group do not include patients with MCL. BR, bendamustine/rituximab; CVP, cyclophosphamide, vincristine, and prednisone; iNHL, indolent non-Hodgkin lymphoma; MCL, mantle cell lymphoma; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. Flinn I et al. ASCO abstract 7500. *J Clin Oncol.* 2017;35(15 suppl).³

study at the ASCO meeting and the ICML.³ The evaluable population included 213 patients in the bendamustine/rituximab arm and 206 in the immunochemotherapy arm. Median follow-up was 65.0 months for the bendamustine/rituximab arm and 64.1 months for the immunochemotherapy arm. Five-year PFS was 65.5% for patients in the bendamustine/rituximab arm vs 55.8% for patients in the immunochemotherapy arm (HR, 0.61; 95% CI, 0.45-0.85; $P=.0025$). When stratified by lymphoma type, 5-year PFS in patients with indolent NHL was 70.3% with bendamustine/rituximab vs 62.0% with R-CHOP or R-CVP (HR, 0.70; 95% CI, 0.49-1.01; $P=.0582$; Figure 5). In patients with mantle cell lymphoma, 5-year PFS was 39.7% with bendamustine/rituximab vs 14.2% with immunochemotherapy (HR, 0.40; 95% CI, 0.21-0.75; $P=.0035$).

Duration of response was 65.5 months in the bendamustine/rituximab arm vs 56.9 months in the R-CHOP/R-CVP arm (HR, 0.66; 95% CI, 0.47-0.92; $P=.0134$). The 5-year duration of response for patients

with indolent NHL was 70.5% with bendamustine/rituximab vs 62.4% with standard treatment (HR, 0.73; 95% CI, 0.50-1.07; $P=.1051$). In patients with mantle cell lymphoma, the 5-year duration of response was 39.7% with bendamustine/rituximab vs 15.9% with R-CHOP/R-CVP (HR, 0.47; 95% CI, 0.24-0.91; $P=.0231$). The 5-year overall survival for the entire cohort was 81.6% with bendamustine/rituximab vs 85.0% with immunochemotherapy (HR, 1.15; 95% CI, 0.72-1.84; $P=.5461$). The 5-year overall survival was similar for both treatments in the subgroups of patients with indolent NHL ($P=.3316$) and mantle cell lymphoma ($P=.6894$). The 5-year event-free survival was superior with bendamustine/rituximab vs immunochemotherapy for the overall study population ($P=.002$) and for mantle cell lymphoma patients ($P=.0005$), but the difference was not significant for patients with indolent NHL ($P=.0944$).

Maintenance treatment with rituximab was administered to 43% of patients in the bendamustine/rituximab arm and 45% of patients in the

control arm. Twenty-two percent of patients in the bendamustine/rituximab arm received second-line treatment vs 34% in the R-CHOP/R-CVP arm.

There were 40 deaths in the bendamustine/rituximab arm and 32 in the R-CHOP/R-CVP arm. Causes of death included disease progression (16 in the bendamustine/rituximab arm and 16 in the R-CHOP/R-CVP arm), complications associated with SCT or reason not reported (3 vs 6), cardiovascular events (7 vs 2), respiratory events (3 vs 1), infection (6 vs 3), and secondary malignancy excluding transformed NHL (5 vs 3). In an exploratory analysis, secondary malignancies were more frequent among patients treated with bendamustine/rituximab (19% vs 11%; $P=.022$). Secondary malignancies included transformed NHL/DLBCL (5 cases in the bendamustine/rituximab arm vs 7 in the R-CHOP/R-CVP arm), basal cell carcinoma (9 vs 4), squamous cell carcinoma of the skin (12 vs 2), melanoma (2 vs 1), myelodysplastic syndrome (1 vs 1), and other solid malignancies (19 vs 11).

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Brentuximab Vedotin Consolidation to Reduce Radiation Use in Patients With Limited Stage Non-Bulky Hodgkin Lymphoma: an Update From a Phase 2 Clinical Trial

HL accounts for 16% of cancers in patients ages 15 to 24 years.¹ Standard treatment for limited-stage HL consists of 4 to 6 cycles of chemotherapy, with or without consolidation radiotherapy. Although standard treatment cures approximately 90% of patients with limited-stage HL, some patients have a diminished lifespan or other delayed, treatment-related complications, such as secondary malignancies and cardiovascular disease. At the ICML, Dr Steven Park presented updated results from a multicenter phase 2 trial that investigated induction treatment with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by consolidation with brentuximab vedotin in patients with treatment-naive, limited-stage, nonbulky HL.² The primary objective was to determine the proportion of patients with PET-negative disease after study treatment, with a goal of achieving PET negativity and avoiding radiation in at least 85% of patients. Patients initially received 2 cycles of ABVD followed by interim PET imaging. Patients with favorable disease and a negative PET scan proceeded to consolidation with brentuximab vedotin (1.8 mg/kg) administered once every 3 weeks for 6 cycles. The remaining patients received an additional 2 to 4 cycles of ABVD, depending on risk factors and PET imaging results, and then received consolidation with brentuximab vedotin.

The 40 evaluable patients had a median age of 29 years (range, 19-68 years), and 45% had unfavorable disease. Most patients (92.5%) received 4 or fewer cycles of ABVD, and 27.5% received 2 cycles. One patient was treated with radiation for progressive disease. Toxicities of grade 3 or higher associated with brentuximab vedotin included neutropenia (7.5%), peripheral neuropathy (2.5%), and rash (2.5%). One patient developed pancreatitis and died from sepsis and hepatic failure. Pancreatitis and sepsis are rare, known complications associated with brentuximab vedotin.

After 2 cycles of ABVD, 72.5% of patients achieved PET-negative disease, as determined by a Deauville score of less than 3 (Table 3). After completion of brentuximab vedotin consolidation therapy, 37 of 39 evaluable patients (94.9%) had PET-negative disease. After a median follow-up

of 22 months, estimated 2-year PFS was 92%, and estimated 2-year overall survival was 97%. Among the 37 patients who achieved PET-negative disease at the end of brentuximab vedotin treatment, all avoided radiation and remained in remission, and these patients had an estimated 2-year PFS of 100%. The authors concluded that, in patients with nonbulky, limited-stage HL, consolidation with brentuximab vedotin may enable reduced use of radiation therapy while achieving excellent survival outcomes for the majority of patients.

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Table 3. Outcome in Patients With Hodgkin Lymphoma Treated With ABVD Followed by Consolidation With Brentuximab Vedotin

	Interim-PET2 (n=40) ^a	Post-Brentuximab Vedotin ^b
Deauville 1	13	18
Deauville 2	16	19
Deauville 3	8	1
Deauville ≥4	3	1

^aThe PET scan was administered after 2 cycles of ABVD.

^bThe PET scan was administered after 6 cycles of brentuximab vedotin.

ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; PET, positron emission tomography. Adapted from Park SI et al. ICML abstract 070. *Hematol Oncol*. 2017;35(suppl S2).²

Highlights in Lymphoma From the 2017 ASCO Meeting and the 14th ICML: Commentary

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Several studies in lymphoma presented at the 2017 American Society of Clinical Oncology (ASCO) meeting and the 14th International Conference on Malignant Lymphoma (ICML) have the potential to impact practice. New data and updated analyses were presented on copanlisib, tazemetostat, brentuximab vedotin, chimeric antigen receptor (CAR) T-cell therapy, bendamustine, and lenalidomide.

Copanlisib

At the ICML, Dr Martin Dreyling presented results from the pivotal phase 2 CHRONOS-1 trial, which evaluated copanlisib in patients with relapsed or refractory indolent lymphoma.¹ The study population included patients with the indolent lymphomas: follicular lymphoma, marginal zone lymphoma, or small lymphocytic lymphoma. CHRONOS-1 can be viewed as the registration trial for copanlisib, which is a pan-class I phosphoinositide 3-kinase inhibitor. Unfortunately, copanlisib is given intravenously and not orally. The difficult dosing schedule consists of 60 mg administered intravenously on days 1, 8, and 15 of a 28-day cycle.

The trial included 142 patients. The overall response rate was nearly 60%, and the complete response rate was 12%. Data were similar across the subtypes of lymphoma. The clinical benefit rate was nearly 91%. Copanlisib was fairly well-tolerated. There was a 14% incidence of lung-related issues, either infection or pneumonitis. Colitis was minimal. It seems likely

that these data will lead the US Food and Drug Administration to approve copanlisib in patients with relapsed or refractory indolent lymphoma.

Tazemetostat

At the ICML plenary session, Dr Franck Morschhauser discussed results from a phase 2 multicenter study of the *EZH2* inhibitor tazemetostat in patients with relapsed or refractory non-Hodgkin lymphoma.² The study had 4 cohorts: follicular lymphoma with an *EZH2* mutation; follicular lymphoma without the mutation, but with increased expression of the protein; diffuse large B-cell lymphoma (DLBCL) with the mutation; and DLBCL without the mutation. Tazemetostat is administered orally twice a day.

The study enrolled more than 165 patients. The highlight of the data was an 85% response rate in patients with follicular lymphoma and the *EZH2* mutation. Patients with DLBCL and the mutation had a response rate of only 29%. Tazemetostat was fairly well-tolerated. Occasional thrombocytopenia was seen. This therapy and similar agents that target *EZH2* will be extensively studied over the next year, and it is expected that they will be approved in NHL.

Brentuximab Vedotin

Several studies evaluated brentuximab vedotin in various aspects of Hodgkin lymphoma management. In the BREVITY trial, brentuximab vedotin was given as first-line treatment in patients who were unsuitable for standard chemotherapy.³ The

patients' median age was 76 years, and their characteristics were typical for an elderly population. The study followed a standard Simon 2-phase design. The primary endpoint was complete response rate. Patients received the standard dose of brentuximab vedotin.

The trial provided data for 30 evaluable patients. Unfortunately, the median number of cycles was only 4, and 14 patients had to stop treatment because of toxicity or other adverse events. The overall response rate was 84%. The complete metabolic response after 4 cycles of brentuximab vedotin was only 26%, which did not meet the predefined level of 40%. It appears that single-agent brentuximab vedotin will not become a standard treatment option in this patient population.

A second study tested whether brentuximab vedotin can replace radiotherapy in patients with limited, early-stage Hodgkin lymphoma.⁴ This multicenter phase 2 study enrolled 41 patients. The primary endpoint was the rate of patients without disease according to positron emission tomography (PET) after doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by brentuximab vedotin. Nearly all the patients had a complete response. For this regimen to move forward, a randomized trial must compare maintenance with brentuximab vedotin vs radiation therapy.

Two updates were provided for trials evaluating brentuximab vedotin and nivolumab. These trials were previously presented at the 2016 American Society of Hematology (ASH) meeting.^{5,6} Dr Alex Herrera presented

updated results from a study of brentuximab vedotin and nivolumab used as a pretransplant salvage regimen.⁷ Dr Catherine Diefenbach presented data on the use of brentuximab vedotin and nivolumab as a palliative regimen in patients with relapsed/refractory Hodgkin lymphoma, some of whom had undergone stem cell transplant.⁸

After 6 further months of follow-up, both of these studies continued to show a stable complete response rate exceeding 60%. This regimen, administered in the outpatient setting, was well-tolerated. There is always a concern regarding pneumonitis when these drugs are combined, but that incidence thus far was low. The initial results of the study by Dr Herrera appear consistent with previous reports of studies using standard platinum-based salvage chemotherapy, and this approach may be less toxic.⁷ The study will provide posttransplant data when they are mature. The study by Dr Diefenbach is now adding ipilimumab to the brentuximab vedotin/nivolumab platform in an effort to improve the complete response rate.⁸

My colleagues and I at Memorial Sloan Kettering Cancer Center presented results from a study that evaluated whether baseline metabolic tumor volume can be used as a pretransplant risk factor in patients with relapsed or refractory Hodgkin lymphoma.⁹ Many previous studies have found that a negative pretransplant PET scan predicts for outcome and cure after autologous stem cell transplant.¹⁰ Our study found that a presalvage metabolic tumor volume of less than 109.5 cm³ was associated with a cure in 44 of 48 patients. Among the 12 patients with a higher metabolic tumor volume, only 4 were in remission. Future studies will be needed to confirm the association. However, this risk factor can be a tool for nuclear medicine physicians. In theory, patients with low baseline metabolic tumor volume at the time of relapse may be able to avoid stem cell transplant. This is a research question, however, and one must keep in mind

that nearly 85% of patients with low metabolic tumor volume were cured with high-dose therapy/autologous stem cell transplant.

CAR T-Cell Therapy

There were several studies of CAR-modified T cells. At the ASCO meeting, Dr Jeremy Abramson discussed a multicenter trial of JCAR017, a second-generation, CD19-directed, 4-1BB CAR-modified T-cell product.¹¹ JCAR017 uses both CD8 and CD4 in a 1:1 ratio. The study enrolled patients with relapsed/refractory DLBCL, grade 3 follicular lymphoma, mantle cell lymphoma, or primary mediastinal B-cell lymphoma. All patients underwent standard lymphodepletion with fludarabine and cyclophosphamide.

This ongoing study has enrolled 54 patients. Dr Abramson presented data for patients with DLBCL. Two patients developed severe cytokine-release syndrome. Severe neurotoxicity occurred in 16 patients. Thus far, the overall response rate was 76%, and 52% of the patients achieved a complete response. The follow-up is short, however, at 3 months. Further follow-up will be necessary to determine whether the complete responses are durable.

At the ICML, Dr Craig Sauter presented results of a phase 1 trial of 19-28z in patients with relapsed or refractory B-cell non-Hodgkin lymphoma who had been treated with high-dose therapy and autologous stem cell transplant.¹² The aim was to use 19-28z to target minimal residual disease. Among the 15 patients who were treated, 10 experienced toxicity: either grade 2 to 4 neurotoxicity or cytokine release syndrome. These toxicities were reversible with tocilizumab and corticosteroids. The study had a long median follow-up of 31 months. Unfortunately, the 2-year progression-free survival was only 30%, the same as that seen in patients with DLBCL who undergo standard autologous transplant.

When comparing these 2 studies, it should be remembered that these

CAR T-cell therapies are different constructs. The study by Dr Abramson had patients with significant amounts of tumor vs minimal residual disease, which may be related to both the response rates as well as the toxicity profile.¹¹ This study is continuing to enroll patients. The idea of giving CAR-modified T cells after autologous stem cell transplant is likely not sustainable.

Bendamustine

At ASCO, there were 2 important presentations evaluating bendamustine and rituximab. Dr Ian Flinn provided 5-year follow-up data for the BRIGHT study, which compared bendamustine and rituximab vs rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or rituximab plus cyclophosphamide, vincristine, and prednisone (R-CVP) in patients with untreated indolent lymphoma.¹³ The 5-year data suggested that there was no difference in overall survival between any of the treatments. The progression-free survival was clearly improved by bendamustine and rituximab among patients with mantle cell lymphoma. For the other subtypes of lymphoma, however, only marginal improvement was seen with the bendamustine/rituximab combination. An interesting observation was that the toxic death rate was higher in the bendamustine/rituximab arm, which might be secondary to an increased risk of secondary cancers.

It is fairly clear from this data set that bendamustine/rituximab was superior to R-CVP. Bendamustine/rituximab had similar results, however, to R-CHOP. Physicians must decide on their optimal program for indolent lymphoma, as they have more than one choice.

Dr Mathias Rummel presented 10-year follow-up data from the StiL study, which compared bendamustine and rituximab vs R-CHOP in patients with indolent lymphomas.¹⁴ The analysis included 420 patients who were evaluable for response. Nearly

two-thirds of patients had follicular lymphoma. Bendamustine and rituximab improved progression-free survival in the entire cohort, with a highly significant hazard ratio of 0.58. This improvement was driven primarily by patients with mantle cell lymphoma and follicular lymphoma. The time to next treatment was also superior for bendamustine and rituximab vs R-CHOP. However, there was no difference in overall survival. Important prognostic factors were a complete response, elevated levels of lactate dehydrogenase, and a poor-risk score on the Follicular Lymphoma International Prognostic Index. There was also no difference in secondary malignancies. This data set suggests that the combination of bendamustine and rituximab offers patients a long-term improvement in progression-free survival. However, in my opinion, neither of the bendamustine/rituximab studies is so convincing that this treatment should always be the first choice of therapy for these lymphoma subtypes.

Dr Paula Cramer and colleagues evaluated bendamustine followed by obinutuzumab and venetoclax in patients with chronic lymphocytic leukemia. Results were presented at the ICML plenary session.¹⁵ This open-label phase 2 study employed an interesting strategy: bendamustine was given for debulking, and then followed by obinutuzumab and venetoclax in induction and maintenance. The primary endpoint was overall response rate, and the secondary endpoint was minimal residual disease. The analysis included 34 patients who were treatment-naïve and 29 with relapsed/refractory disease. The patient population was well-balanced, and 19% had the 17p abnormality. Among the patients who started treatment, 60 were able to complete all courses. The overall response rate was nearly 100%. Six patients had a complete response, and 36 had a partial response. An interesting finding was that 89% of patients were negative for minimal residual disease by flow cytometry in

the peripheral blood. The treatment regimen was well-tolerated, and it will likely move forward into a randomized trial.

Lenalidomide Plus Rituximab

The randomized phase 3b MAGNIFY study evaluated lenalidomide plus rituximab followed by maintenance therapy in 234 patients with follicular lymphoma, marginal zone lymphoma, or mantle cell lymphoma.¹⁶ All patients were first treated with lenalidomide plus rituximab. Patients who responded were then randomly assigned to maintenance with lenalidomide plus rituximab or rituximab alone. Dr David Andorsky provided data for 128 evaluable patients with follicular lymphoma.¹⁶ Patients had previously received bendamustine and rituximab or regimens incorporating R-CHOP or R-CVP. These patients had experienced an early relapse or were double-refractory (to both rituximab and chemotherapy). The overall response rate was very respectable, at 45% in those with double-refractory disease and 47% in the early-relapsed patients. The complete response rate was 21% in both groups. The median duration of response had not been reached. These results are encouraging, and the study continues to enroll patients.

Disclosure

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