Clinical Advances in
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Highlights in Lymphoma From the 2011 American Society of Hematology (ASH) Annual Meeting

December 10–13, 2011 • San Diego, California

- Frontline Therapy With Brentuximab Vedotin Combined With ABVD or AVD in Newly Diagnosed Advanced Stage Hodgkin Lymphoma
- Brentuximab Vedotin in Systemic Anaplastic Large Cell Lymphoma
- Ponatinib in Patients With Chronic Myeloid Leukemia and Acute Lymphoblastic Leukemia
- Analysis of Patients With Common PTCL Subtypes From a Phase II Study of Romidepsin
- Obinutuzumab Monotherapy in Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

PLUS Meeting Abstract Summaries

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ADCETRIS is the first approved CD30-directed antibody-drug conjugate (ADC)

CD30-DIRECTED

ADCETRIS™

brentuximab vedotin

Indicated for the treatment of:

- Hodgkin lymphoma (HL) after failure of autologous stem cell transplant (ASCT)[1]
- HL in patients who are not ASCT candidates after failure of at least 2 multiagent chemotherapy regimens[1]
- Systemic anaplastic large cell lymphoma (sALCL) after failure of at least 1 multiagent chemotherapy regimen[1]

The indications for ADCETRIS are based on response rate. There are no data available demonstrating improvement in patient-reported outcomes or survival with ADCETRIS.[1]

A therapeutic alternative for relapsed patients
73% objective response rate (95% CI: 65%-83%) in **HL**[1]
86% objective response rate (95% CI: 77%-95%) in **sALCL**[1]

BOXED WARNING

Progressive multifocal leukoencephalopathy (PML): JC virus infection resulting in PML and death can occur in patients receiving ADCETRIS.[1]

Contraindication

Concomitant use of ADCETRIS and bleomycin is contraindicated due to pulmonary toxicity.[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. Treating physicians should monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness and institute dose modifications accordingly.[1]

Infusion reactions

Infusion-related reactions, including anaphylaxis, have occurred with ADCETRIS. Monitor patients during infusion. If an infusion reaction occurs, the infusion should be interrupted and appropriate medical management instituted. If anaphylaxis occurs, the infusion should be immediately and permanently discontinued and appropriate medical management instituted.[1]

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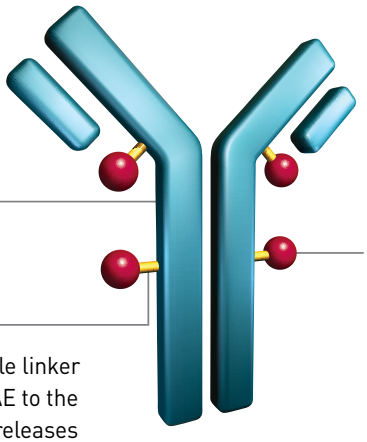
ADCETRIS is an ADC designed to target cells expressing CD30[1]



Antibody

The antibody, brentuximab, specific for CD30[1]

Linker

A synthetic protease-cleavable linker that covalently attaches MMAE to the CD30-directed antibody and releases the agent within the target cell[1]

Cytotoxic agent

The synthetic microtubule-disrupting agent, monomethyl auristatin E (MMAE, vedotin), that induces target cell death[1]

CD30 is prevalent in both HL and sALCL[2]

- Binding of ADCETRIS to CD30 on the cell surface initiates internalization of the ADC-CD30 complex[1]
- Inside the cell, MMAE is released via proteolytic cleavage[1]
- Binding of released MMAE to tubulin disrupts the microtubule network, inducing apoptotic cell death[1]

Single-agent ADCETRIS was evaluated in two pivotal, phase 2, open-label, single-arm, multicenter trials:

- 102 patients with HL who relapsed after ASCT[1]
- 58 patients with relapsed sALCL[1]

ADCETRIS 1.8 mg/kg was administered intravenously over 30 minutes every 3 weeks.[1]

Assessment of efficacy included objective response rate (complete remission plus partial remission) and duration of response evaluated by an independent review facility based on measures defined in the 2007 Revised Response Criteria for Malignant Lymphoma (modified).[1,3]

Neutropenia

Monitor complete blood counts prior to each dose of ADCETRIS and consider more frequent monitoring for patients with Grade 3 or 4 neutropenia. If Grade 3 or 4 neutropenia develops, manage by dose delays, reductions or discontinuation. Prolonged (≥1 week) severe neutropenia can occur with ADCETRIS.[1]

Tumor lysis syndrome

Patients with rapidly proliferating tumor and high tumor burden are at risk of tumor lysis syndrome and these patients should be monitored closely and appropriate measures taken.[1]

Progressive multifocal leukoencephalopathy (PML)

JC virus infection resulting in PML and death has been reported in ADCETRIS-treated patients. 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. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture or brain biopsy. Hold ADCETRIS if PML is suspected and discontinue ADCETRIS if PML is confirmed.[1]

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ADCETRIS induced complete and partial remissions in clinical trials[1]

Efficacy in relapsed patients[1]

	Relapsed HL (N = 102) Median treatment duration: 27 weeks			Relapsed sALCL (N = 58) Median treatment duration: 24 weeks		
	Response, % (95% CI)	Duration of response in months		Response, % (95% CI)	Duration of response in months	
		Median (95% CI)	Range		Median (95% CI)	Range
Complete remission (CR)	32 (23-42)	20.5 (12.0-NE*)	1.4-21.9+	57 (44-70)	13.2 (10.8-NE*)	0.7-15.9+
Partial remission (PR)	40 (32-49)	3.5 (2.2-4.1)	1.3-18.7	29 (18-41)	2.1 (1.3-5.7)	0.1-15.8+
Objective response rate (ORR)	73 (65-83)	6.7 (4.0-14.8)	1.3-21.9+	86 (77-95)	12.6 (5.7-NE*)	0.1-15.9+

*Not estimable. +Follow-up was ongoing at the time of data submission.

- ADCETRIS demonstrated efficacy in sALCL patients with poor prognosis[1]
  - 72% of sALCL patients had anaplastic lymphoma kinase (ALK)-negative disease, which has a worse prognosis than ALK-positive disease[1,4]

Adverse reactions occurring in ≥20% of patients regardless of causality[1]

	HL (N = 102)			sALCL (N = 58)		
	% of patients			% of patients		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Neutropenia	54	15	6	55	12	9
Peripheral sensory neuropathy	52	8	-	53	10	-
Fatigue	49	3	-	41	2	2
Nausea	42	-	-	38	2	-
Anemia	33	8	2	52	2	-
Upper respiratory tract infection	47	-	-	12	-	-
Diarrhea	36	1	-	29	3	-
Pyrexia	29	2	-	38	2	-
Rash	27	-	-	31	-	-
Thrombocytopenia	28	7	2	16	5	5
Cough	25	-	-	17	-	-
Vomiting	22	-	-	17	3	-

- 21% of patients discontinued therapy due to treatment-emergent adverse reactions[1]

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brentuximab vedotin

Continue treatment until a maximum of 16 cycles, disease progression or unacceptable toxicity[1]

Recommended dose is 1.8 mg/kg administered only as an IV infusion over 30 minutes every 3 weeks[1]

- Patients who have experienced a prior infusion-related reaction should be premedicated for subsequent infusions[1]
- Complete blood counts should be monitored prior to each dose of ADCETRIS[1]

Most PN was Grade 1 or 2—no Grade 4 PN events were observed[1]

- 54% of patients experienced peripheral neuropathy (PN) in the pivotal trials[1]
- Grade 3 PN (sensory) was reported by 8% and 10% of patients in the HL and sALCL trials, respectively[1]
  - 8% discontinued due to peripheral sensory neuropathy[1]
- Grade 3 PN (motor) was reported by 4% and 3% of patients in the HL and sALCL trials, respectively[1]
  - 3% discontinued due to peripheral motor neuropathy[1]

Monitor patients for PN and institute dose modification accordingly[1]

New or worsening Grade 2 or 3	Hold dose until PN improves to Grade 1 or baseline and then restart at 1.2 mg/kg
Grade 4	Discontinue ADCETRIS

Improvement or resolution of PN symptoms was observed in the majority of patients during follow-up[1]:

- 49% had complete resolution
- 51% had residual PN at time of last evaluation (31% partial improvement, 20% no improvement)

Neutropenia should be managed by dose delay and reduction[1]

Grade 3 or 4	Hold dose until resolution to baseline or Grade 2 or lower Consider growth factor support for subsequent cycles
Recurrent Grade 4 despite use of growth factors	Discontinue or reduce dose to 1.2 mg/kg

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REFERENCES: 1. ADCETRIS [Prescribing Information]. Bothell, WA: Seattle Genetics Inc; 2012. **2.** Haluska FG, Brufsky AM, Canellos GP. The cellular biology of the Reed-Sternberg cell. *Blood.* 1994;84(4):1005-1019. **3.** Cheson BD, Pfistner B, Juweid ME, et al; International Harmonization Project on Lymphoma. Revised response criteria for malignant lymphoma. *J Clin Oncol.* 2007;25(5):579-586. **4.** Savage KJ, Harris NL, Vose JM, et al; International Peripheral T-Cell Lymphoma Project. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. *Blood.* 2008;111(12):5496-5504.

US/BV/2011/0029b

CD30-DIRECTED

ADCETRIS™

brentuximab vedotin

Brief Summary of Prescribing Information

(see Package Insert for full Prescribing Information)

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

JC virus infection resulting in PML and death can occur in patients receiving ADCETRIS.

Indications and usage

These indications are based on response rate. There are no data available demonstrating improvement in patient reported outcomes or survival with ADCETRIS.

ADCETRIS (brentuximab vedotin) is indicated for treatment of patients with Hodgkin lymphoma (HL) after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates.

ADCETRIS is indicated for treatment of patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen.

Contraindications

Pulmonary toxicity: Concomitant use of ADCETRIS and bleomycin is contraindicated due to pulmonary toxicity. In a clinical trial 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.

Warnings and precautions

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 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.

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.

Neutropenia

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. Prolonged (≥1 week) severe neutropenia can occur with ADCETRIS. If Grade 3 or 4 neutropenia develops, manage by dose delays, reductions, or discontinuations.

Tumor lysis syndrome

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

Progressive multifocal leukoencephalopathy

JC virus infection resulting in PML and death has been reported in ADCETRIS-treated patients. 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. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture or brain biopsy. Hold ADCETRIS dosing for any suspected case of PML and discontinue ADCETRIS dosing if a diagnosis of PML is confirmed.

Stevens-Johnson syndrome

Stevens-Johnson syndrome has been reported with ADCETRIS. If Stevens-Johnson syndrome occurs, discontinue ADCETRIS and administer appropriate medical therapy.

Use in pregnancy

There are no adequate and well-controlled studies of ADCETRIS in pregnant women. However, based on its mechanism of action and findings in animals, ADCETRIS can cause fetal harm when administered to a pregnant woman. Brentuximab vedotin caused embryo-fetal toxicities, including significantly decreased embryo viability and fetal malformations, in animals at maternal exposures that were similar to human exposures at the recommended doses for patients with HL and sALCL. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving the drug, the patient should be apprised of the potential hazard to the fetus.

Adverse reactions

ADCETRIS was studied as monotherapy in 160 patients in two phase 2 trials. Across both trials, the most common adverse reactions (≥10%), regardless of causality, were neutropenia, anemia, thrombocytopenia, lymphadenopathy, peripheral sensory neuropathy, peripheral motor neuropathy, headache, dizziness, fatigue, pyrexia, chills, pain, edema peripheral, upper respiratory tract infection, nausea, diarrhea, abdominal pain, vomiting, constipation, rash, pruritis, alopecia, night sweats, dry skin, cough, dyspnea, oropharyngeal pain, arthralgia, myalgia, back pain, pain in extremity, muscle spasms, insomnia, anxiety, decreased appetite and weight decreased.

ADCETRIS was studied in 102 patients with 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 27 weeks (range, 3 to 56 weeks). The most common adverse reactions (≥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. The most common serious adverse reactions experienced by patients with HL include peripheral motor neuropathy (4%), abdominal pain (3%), pulmonary embolism (2%), pneumonitis (2%), pneumothorax (2%), pyelonephritis (2%), and pyrexia (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 24 weeks (range, 3 to 56 weeks). The most common adverse reactions (≥20%), regardless of causality, were neutropenia, anemia, peripheral sensory neuropathy, fatigue, nausea, pyrexia, rash, diarrhea, and pain. 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%).

Drug interactions

In vitro data indicate that monomethyl auristatin E (MMAE) is a substrate and an inhibitor of CYP3A4/5.

Effect of other drugs on ADCETRIS

CYP3A4 Inhibitors/Inducers: 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%.

Effect of ADCETRIS on other drugs

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.

Use in specific populations

Pregnancy

Pregnancy Category D. There are no adequate and well-controlled studies with ADCETRIS in pregnant women. However, based on its mechanism of action and findings in animals, ADCETRIS can cause fetal harm when administered to a pregnant woman. Brentuximab vedotin caused embryo-fetal toxicities in animals at maternal exposures that were similar to human exposures at the recommended doses for patients with HL and sALCL. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

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

Nursing mothers

It is not known whether brentuximab vedotin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ADCETRIS a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use

The safety and effectiveness of ADCETRIS have not been established in the pediatric population. Clinical trials of ADCETRIS included only 9 pediatric patients and this number is not sufficient to determine whether they respond differently than adult patients.

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. Safety and efficacy have not been established.

Renal impairment

The kidney is a route of excretion for MMAE. The influence of renal impairment on the pharmacokinetics of MMAE has not been determined.

Hepatic impairment

The liver is a route of clearance for MMAE. The influence of hepatic impairment on the pharmacokinetics of MMAE has not been determined.

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.

Dosage and administration

General dosing information

The recommended dose is 1.8 mg/kg administered only as an intravenous infusion over 30 minutes every 3 weeks. The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg. Do not administer as an intravenous push or bolus. Continue treatment until a maximum of 16 cycles, disease progression or unacceptable toxicity.

Dose modification

Peripheral Neuropathy: Peripheral neuropathy should be managed using a combination of dose delay and reduction to 1.2 mg/kg. 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: Neutropenia should be managed by dose delays and reductions. The dose of ADCETRIS should be held for Grade 3 or 4 neutropenia until resolution to baseline or Grade 2 or lower. Growth factor support should be considered for subsequent cycles in patients who experience Grade 3 or 4 neutropenia. In patients with recurrent Grade 4 neutropenia despite the use of growth factors, discontinuation or dose reduction of ADCETRIS to 1.2 mg/kg may be considered.

SeattleGenetics®

Frontline Therapy With Brentuximab Vedotin Combined With ABVD or AVD in Patients With Newly Diagnosed Advanced Stage Hodgkin Lymphoma

Up to 30% of patients with Hodgkin lymphoma will not achieve a long-term remission with conventional therapy.[1] Hodgkin lymphoma is characterized by the presence of CD30-positive Hodgkin Reed-Sternberg cells. Brentuximab vedotin is an antibody-drug conjugate consisting of an anti-CD30 monoclonal antibody linked through a protease cleavable linker to the microtubule disrupting agent monomethyl auristatin E (MMAE; Figure 1). Microtubule disruption leads to cell cycle arrest and apoptosis.

In 2011, brentuximab vedotin was approved by the US Food and Drug Administration (FDA) for the treatment of Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least 2 prior multi-agent chemotherapy regimens in patients who are not ASCT candidates. The drug was also approved for the treatment of patients with systemic anaplastic large cell lymphoma (ALCL) after failure of at least 1 prior multi-agent chemotherapy regimen.

The approval in Hodgkin lymphoma was based on results of a single-arm, open-label, multicenter phase II study in 102 patients with relapsed or refractory Hodgkin disease after ASCT.[2] In that trial, brentuximab vedotin was associated with an objective response rate of 75%, including 34% complete remissions.

Other studies are evaluating the use of brentuximab vedotin in additional settings. At the American Society of Hematology (ASH) 2011 meeting, Younes and colleagues presented initial results of an open-label phase I study evaluating the addition of brentuximab vedotin to combination chemotherapy with the standard first-line regimen of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) or a modified regimen without bleomycin (AVD) in patients with previously untreated advanced-stage Hodgkin lymphoma.[3] Study objectives included the safety profile, the maximum tolerated dose of brentuximab vedotin in this setting, and the antitumor activity.

The study enrolled 45 treatment-naïve patients ages 18–60 years with advanced-stage Hodgkin lymphoma, defined as bulky stage IIA disease or stage IIb, III, or IV disease. Patients received a standard dosing schedule of ABVD plus brentuximab vedotin at 0.6, 0.9, or 1.2 mg/kg (25 patients) or brentuximab vedotin 1.2 mg/kg with AVD (20 patients). Regimens were administered on Days 1 and 15 of 28-day cycles for 6 cycles, for a total of 12 doses of brentuximab vedotin. Radiation therapy was allowed at the investigators' discretion.

In this interim analysis, Dr. Younes presented findings from the first 44 patients enrolled in the study. Among these patients, the median age was 32 years; 23% of patients had an International Prognostic Index (IPI) score of 4 or higher, and 45% had stage IV disease.

Adverse events were primarily related to the combination chemotherapy. The most common adverse events included neutropenia (77%) and nausea (66%). Peripheral sensory neuropathy, fatigue, vomiting, and constipation also occurred. Sensory neuropathy was entirely grade 1/2. The combination of brentuximab vedotin and ABVD was associated with a significant risk of pulmonary toxicity, which was observed in 40% of patients. Pulmonary toxicity typically occurred during cycles 3–6 and was reversible in 9 of 10 patients; 7 of 10 patients discontinued bleomycin and were able to continue with the brentuximab vedotin plus AVD. No dose-limiting toxicities were observed. The maximum tolerated dose, and the recommended dose for additional studies, was 1.2 mg/kg in combination with AVD. This dose

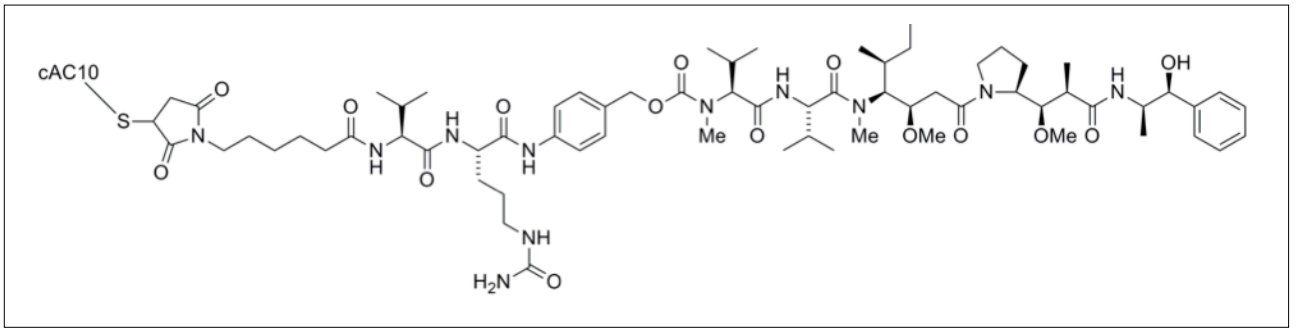

Figure 1. The structure of brentuximab vedotin, an antibody-drug conjugate consisting of an anti-CD30 monoclonal antibody linked through a protease cleavable linker to the microtubule disrupting agent monomethyl auristatin E.

administered every 2 weeks is equivalent to the currently approved dose of 1.8 mg/kg administered every 3 weeks.

Efficacy data were available from the first 15 patients who completed 6 cycles of therapy. All of these patients had received brentuximab vedotin plus ABVD, and all patients achieved complete remission. Moreover, all patients had no evidence of disease by positron emission tomography (PET) scan after 2 cycles. Of the patients in the AVD cohort, 93% achieved PET negativity after 2 cycles.

In summary, the preliminary findings from the phase I study suggest that brentuximab vedotin plus AVD is generally well tolerated. No dose-limiting toxicity was observed at a maximum planned dose of 1.3 mg/kg brentuximab vedotin. However, concurrent administration of bleomycin and brentuximab vedotin is associated with pulmonary toxicity and is not recommended. A planned phase III trial will compare the efficacy and safety of brentuximab vedotin plus AVD versus standard ABVD.

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2. Chen RW, Gopal AK, Smith SE, et al. Results from a pivotal phase II study of brentuximab vedotin (SGN-35) in patients with relapsed or refractory Hodgkin lymphoma (HL). *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2011;29. Abstract 8031.
3. Younes A, Connors JM, Park SI, Hunder NN, Ansell SM. Frontline therapy with brentuximab vedotin combined with ABVD or AVD in patients with newly diagnosed advanced stage Hodgkin lymphoma. *Blood* (ASH Annual Meeting Abstracts). 2011;118. Abstract 955.

Brentuximab Vedotin (SGN-35) in Patients With Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma: A Phase 2 Study Update

Systemic ALCL is an aggressive, mature T-cell non-Hodgkin lymphoma (NHL) characterized by CD30 expression. ALCL is categorized into 3 subtypes: anaplastic lymphoma kinase (ALK)-positive ALCL, ALK-negative ALCL, and primary cutaneous ALCL. Outcomes are more favorable among patients with ALK-positive ALCL than in those with ALK-negative ALCL, with 5-year overall survival (OS) rates of 58% and 34%, respectively (Figures 2 and 3).[1] First-line chemotherapy for systemic ALCL is often effective, with 76–89% of patients achieving remission with standard chemotherapy.[2] However, approximately half of patients relapse, and there are few available therapies for these patients.

Given the expression of CD30 on ALCL cells, clinical trials were undertaken to evaluate the efficacy and safety of brentuximab vedotin in patients with systemic ALCL. A multicenter, open-label, phase II study evaluated intravenous brentuximab vedotin administered at 1.8 mg/kg every 3 weeks for up to 16 cycles in patients with relapsed or refractory systemic ALCL. At ASH 2011, Advani and colleagues presented updated results from this pivotal trial.[3] Patients older than age 12 with measurable disease and a good performance status were eligible. Among the 58 enrolled patients, the median age was 52 years (range, 14–76 years), and 57% were male. Pathology was confirmed by central review in 97% of patients; 72% of patients had ALK-negative disease. Patients had received a median of 2 prior systemic therapies (range, 1–6); 62% of patients had primary refractory disease, and 50% were refractory to their most recent therapy. Twenty-two percent of patients had not responded to any therapy. Other prior therapies included radiotherapy (45%) and ASCT (26%).

The primary endpoint, objective response rate, was 86%, including 59% complete remissions. Clinical responses to brentuximab vedotin appeared to be durable; the median duration of response was 13.2 months among all responding patients and had not been reached at the time of analysis among patients with a complete response (CR). Subgroup analyses indicated that brentuximab vedotin was active across disease characteristics and treatment histories.

The median progression-free survival (PFS) was 14.5 months with brentuximab vedotin versus 6 months with the last therapy, according to the investigators' review. The PFS did not vary according to ALK status. After a median follow-up of 14.7 months from the first dose, the estimated 1-year OS rate was 70%. The investigators also presented data showing outcomes after stem cell transplant in patients attaining a CR on brentuximab vedotin. Overall, 14 patients went on to receive a stem cell transplant after CR; this group included 5 patients who had previously undergone a transplant. The remaining 20 patients did not go on to transplant; 11 of these patients had

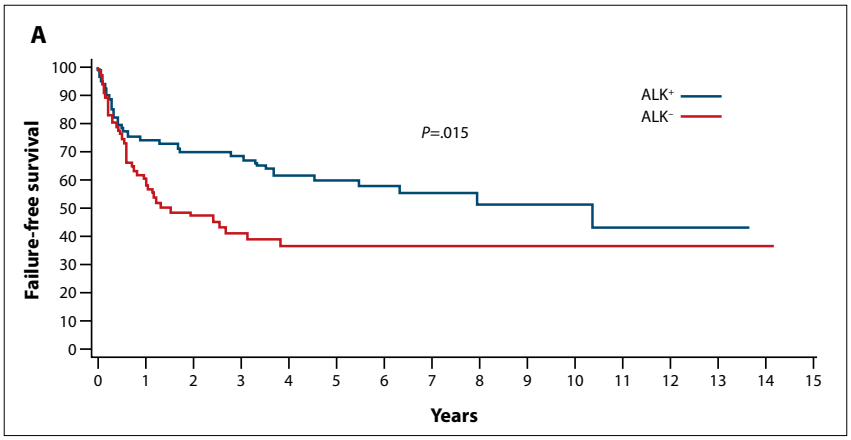

Figure 2. Failure-free survival in systemic anaplastic large cell lymphoma according to ALK status. Adapted from Savage KJ et al. *Blood*. 2008;111:5496-5504.

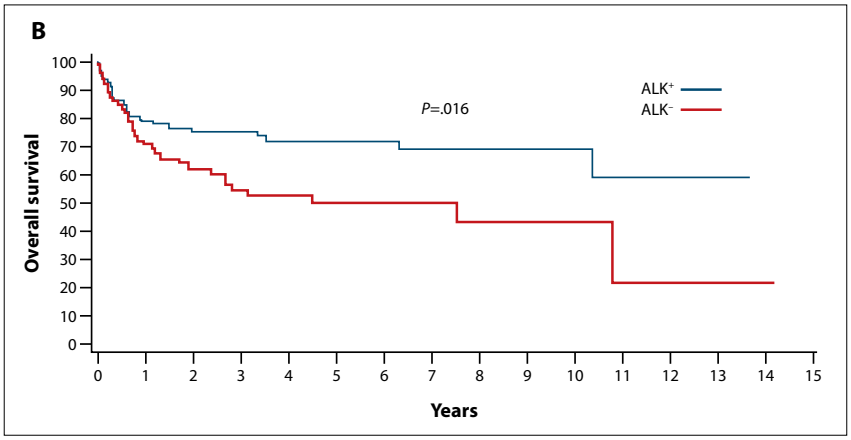

Figure 3. Overall survival in systemic anaplastic large cell lymphoma according to ALK status. Adapted from Savage KJ et al. *Blood*. 2008;111:5496-5504.

previously underwent transplantation.

The median PFS was not reached among those who received an ASCT, 16.9 months among patients who went on to receive a subsequent allogeneic transplant, and 18 months among patients who did not undergo transplantation after attaining a CR on brentuximab vedotin.

Adverse events were primarily grade 1/2. The most common treatment-related adverse event was peripheral neuropathy, reported in 57% of patients. The median time to onset of peripheral neuropathy was 15 weeks. Neuropathy was managed with dose delays and/or dose reductions to 1.2 mg/kg. Approximately 80% of patients had at least some improvement of symptoms. Other adverse events included neutropenia and fatigue.

In conclusion, brentuximab vedotin was associated with durable responses in patients with relapsed or refractory systemic ALCL. Complete remissions appeared durable after completing treatment. Based on these results, an ongoing phase I trial is evaluating brentuximab vedotin in patients with previously untreated systemic ALCL. Other planned or ongoing trials are evaluating brentuximab in other settings of CD30-positive malignancies. One important trial currently in the planning stages is a randomized, phase III trial of brentuximab vedotin in patients with systemic ALCL and other CD30-positive mature T-cell neoplasms.

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Initial Findings From the PACE Trial: A Pivotal Phase 2 Study of Ponatinib in Patients With CML and Ph+ ALL Resistant or Intolerant to Dasatinib or Nilotinib, or With the T315I Mutation

Although the introduction of tyrosine kinase inhibitors (TKIs) has significantly improved outcomes for patients with chronic myeloid leukemia (CML), there are no effective treatments available for patients who fail dasatinib or nilotinib, or for those with the T315I mutation. The new oral pan-BCR-ABL inhibitor ponatinib (AP24534) has demonstrated activity against ABL, other kinases, and the T315I mutation.[1] Through its carbon-carbon triple-bond linker, ponatinib avoids the bulky isoleucine residue that constitutes the T315I mutation, instead attaining favorable contact with the residue. Ponatinib has also demonstrated significant activity against all other mutations tested in the laboratory.

A phase I study demonstrated a favorable toxicity profile with the agent and established the maximum tolerated dose at 45 mg/day.[2] In this study, ponatinib demonstrated clinical activity in patients failing multiple prior therapies and in patients with the T315I mutation. These findings led to the development of the pivotal, phase II PACE (Ponatinib Ph+ ALL and CML Evaluation) trial presented in 2011.[3] The primary objective of this international, single-arm, open-label trial was to establish the efficacy and safety of ponatinib in patients with refractory CML in the chronic, accelerated, or blast phase (CP, AP, or BP), or with Philadelphia-positive acute lymphoblastic leukemia, who were resistant or intolerant to dasatinib or nilotinib or had the T315I mutation.

All patients had baseline assessments for mutations at a central laboratory. Patients with a confirmed T315I mutation were assigned to the T315I cohort, and all other patients were assigned to the non-T315I group, even if they had been diagnosed with T315I at their home institution. The trial enrolled patients resistant to prior treatments or who had no standard treatment. Starting in September 2010, 449 patients were enrolled in the trial.

Patients were assigned to cohorts according to their disease stage and the presence of the T315I mutation. The largest cohort included the 207 patients with chronic-phase CML resistant or intolerant to dasatinib or nilotinib without the T315I mutation. An additional 64 patients with chronic-phase CML had the T315I mutation.

Phase III Randomized Intergroup Trial (SWOG S0016) of CHOP Chemotherapy Plus Rituximab Vs. CHOP Chemotherapy Plus Iodine-131-Tositumomab for the Treatment of Newly Diagnosed Follicular Non-Hodgkin's Lymphoma

Press and colleagues presented results of the randomized, phase III intergroup trial (SWOG S0016) of R-CHOP versus CHOP plus I-131-tositumomab for the treatment of newly diagnosed follicular NHL (Abstract 98). The trial enrolled 554 patients with advanced-stage (bulky stage II or stage III or IV) evaluable follicular lymphoma who had received no prior therapy. Patients were randomly assigned to 6 cycles of CHOP chemotherapy every 3 weeks plus 6 doses of rituximab or 6 cycles of CHOP followed by a dosimetric infusion of tositumomab/I-131-tositumomab, followed by a therapeutic infusion of I-131-tositumomab sufficient to deliver a total body dose of 75 cGy. Baseline characteristics were well-balanced between the arms. After a median follow-up of 4.9 years, there were no significant differences in PFS or OS with CHOP plus radioimmunotherapy (CHOP-RIT) and R-CHOP, with 2-year PFS rates of 80% and 76%, respectively (P=.11), and 2-year OS rates of 93% and 97%, respectively (P=.08). Overall response rates were 86% and 85%, respectively, and CR rates were 46% and 41%, respectively. There were no significant differences between CHOP-RIT and R-CHOP in the incidence of grade 4 hematologic toxicity (30% vs 36%), grade 4 nonhematologic toxicity (1.9% vs 1.5), treatment-related mortality (1.5% vs 0.4%), second malignancies (8.3% vs 8.7%), or acute myelogenous leukemia/myelodysplastic syndromes (2.7% vs 1.1%). The median time-to-progression had not been reached in either arm, and thus PFS and OS outcomes remain to be determined. Moreover, the role of RIT consolidation and maintenance rituximab are unknown, and are being evaluated in the follow-up trial SWOG S0801.

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≈10% refractory rates[1]
≈30% relapse rates after complete response[1]
≈50% of transplants fail[2,3]
Long-term health complications[4]
Reduced survival in some patients initially cured[5]

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The median age of all enrolled patients was approximately 60 years. The majority of patients had refractory disease; only 12% were intolerant to dasatinib or nilotinib. Patients were heavily pretreated: in an analysis of prior therapies including investigational TKIs, 94% had received at least 2 TKIs and 57% had failed at least 3 TKIs. Patients in the T315I cohort were less heavily pretreated, with 64% having received imatinib plus dasatinib or nilotinib.

Among patients with CP-CML, 25% of patients had achieved a major cytogenetic response with their most recent TKI. Among patients in AP-CML or BP-CML, 25–30% of patients had achieved a major hematologic response with their most recent TKIs.

At ASH 2011, Cortes and coworkers presented early study results, after a median follow-up of almost 6 months. Among patients with CP-CML, the primary endpoint, major cytogenetic response, was attained by 47% of patients without T315I and 65% of patients with T315I. Major cytogenetic response rates were 33% and 58%, respectively, and major molecular response rates were 15% and 33%, respectively. Among patients with AP-CML and BP-CML, the primary endpoint of major hematologic response was attained by 40% of patients. In patients resistant or intolerant to imatinib or dasatinib, 74% attained a major hematologic response.

The investigators found a correlation between the extent of prior therapy and the likelihood of response to ponatinib. There was a trend for a higher response rate among patients who had received only 2 approved TKIs. However, even among patients who had received 3 approved TKIs, the complete cytogenetic response rate was 32%. Among patients with T315I mutations, response rates ranged from 61–67% in patients exposed to 1 or 2 prior TKIs to 53% in patients who had received 3 or more TKIs.

A subset analysis according to mutation status showed slightly higher response rates in patients with mutations versus those with no mutations. However, the complete cytogenetic response rate in patients without mutations was 32%, suggesting activity in these patients. Among patients with T315I, the complete cytogenetic response rate was 64% in patients with other mutations and 56% in patients without other mutations. In patients with advanced-stage disease, at least 30% of patients attained a major cytogenetic response, as did 53% of patients with AP-CML and T315I mutations. Complete cytogenetic response rates were 20–25% across these groups.

Brentuximab Vedotin (SGN-35) Enables Successful Reduced Intensity Allogeneic Hematopoietic Cell Transplantation in Relapsed/Refractory Hodgkin Lymphoma

Reduced-intensity conditioning allogeneic hematopoietic cell transplantation (RIC allo-HCT) can induce durable remissions in some patients with relapsed or refractory Hodgkin lymphoma after ASCT. However, many patients are not eligible for RIC allo-HCT due to a lack of disease control prior to transplantation. Chen and associates presented a retrospective analysis of the use of RIC allo-HCT in patients with relapsed/refractory Hodgkin lymphoma after ASCT who received brentuximab vedotin during a clinical trial (Abstract 664). The study included patients who had received brentuximab vedotin at the City of Hope National Medical Center (COH) or the Fred Hutchinson Cancer Research Center (FHCRC)/Seattle Cancer Care Alliance (SCCA). Of the 46 patients enrolled at those 2 institutions, 16 patients (35%) went on to receive RIC allo-HCT, including 12 patients at COH and 5 patients at FHCRC/SCCA. There were some differences in transplant procedures between institutions. In all 12 transplants performed at COH, the conditioning regimen was fludarabine/melphalan; matched related donors were available for 5 patients; 10 patients received tacrolimus/sirolimus graft-versus-host disease (GVHD) prophylaxis; and 2 patients received mycophenolate mofetil (MMF) and cyclosporine (CSP). Of the 4 SCCA transplantations, 3 were haploidentical donor transplantations using fludarabine/cyclophosphamide/2 Gy total-body irradiation conditioning and cyclophosphamide/tacrolimus/MMF for GVHD prophylaxis. The conditioning regimen for the fourth patient was 2 Gy total-body irradiation followed by CSP/MMF prophylaxis. Outcomes after RIC allo-HCT were analyzed separately for the 2 institutions. For the 12 patients treated at COH, the 1-year PFS and 1-year OS were 90% and 100%, respectively, after a median follow-up of 13.2 months. The single case of relapse after transplantation was in a patient who went into the transplant with progressive disease. At SCCA, after a median follow-up of 7.2 months, all 4 patients remained alive and progression-free. Overall rates of acute and chronic GVHD were 25% and 63%, respectively. All acute GVHD was grade 1/2, and extensive chronic GVHD was reported in only 1 patient. Prior exposure to brentuximab did not appear to delay engraftment or increase the risk of EBV or CMV. The investigators concluded that the use of brentuximab vedotin enabled patients to receive RIC allo-HCT, leading to potentially prolonged disease control, without adversely affecting the transplant process or recovery.

Ponatinib was well tolerated, with treatment-related adverse events that were primarily transient, manageable grade 1/2 events. The most common reactions were rash and dry skin, both reported in approximately 30% of patients. In the phase I study, the dose-limiting toxicity was pancreatitis, although this event has not lead to treatment discontinuation in any patients. Lipase elevations were detected in 16% of patients.

Currently, the majority of patients remain on treatment, including 81% of patients with CP-CML. Adverse events have required treatment discontinuation in 8% of patients, primarily due to thrombocytopenia. Overall, 4% of patients have died.

In conclusion, these early results demonstrate substantial clinical activity with ponatinib in patients with heavily pretreated CML or Philadelphia-positive acute lymphoblastic leukemia across a range of patient cohorts. The preliminary results from this study confirm those reported in the phase I study, suggesting significant activity with this agent in patients who have failed multiple prior therapies. Results should continue to improve with a longer duration of therapy. Ponatinib has also demonstrated a favorable safety profile, with few patients discontinuing therapy due to adverse events.

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Analysis of Patients With Common PTCL Subtypes From a Phase II Study of Romidepsin in Relapsed or Refractory PTCL

Peripheral T-cell lymphoma (PTCL) is a rare, heterogeneous group of lymphomas associated with poor responses to chemotherapy, high relapse rates, and poor long-term survival. There is no standard of care for the treatment of PTCL. Romidepsin is a histone deacetylase (HDAC) inhibitor that is approved in the United States for the treatment of patients with cutaneous T-cell lymphoma who have received at least 1 prior systemic therapy and patients with PTCL who have received at least 1 prior therapy.

The approval of romidepsin in PTCL was based in part on findings from a single-arm, open-label, phase II study that demonstrated the benefit of romidepsin in patients with relapsed or refractory PTCL and the tolerability of the agent. In the study, patients with histologically confirmed PTCL who failed, or were refractory to, at least 1 prior systemic therapy received romidepsin 14 mg/m^2 administered over 4 hours on Days 1, 8, and 15 every 28 days for up to 6 cycles. Romidepsin was continued until progression unless patients requested to discontinue treatment.

The primary endpoint was the rate of CR/CR unconfirmed (CRu). Secondary endpoints included overall response rate (ORR) and duration of response. The investigators also evaluated CR and overall response according to PET scan, although not all patients underwent PET scanning.

At ASH 2011, Coiffier and colleagues presented an analysis comparing the efficacy and safety of romidepsin in the study according to PTCL subtype.[1] Of the 130 patients enrolled, the most common subtypes represented were PTCL-not otherwise specified (NOS) (69 patients), angioimmunoblastic T-cell lymphoma (AITL) (27 patients), and ALK-1–negative ALCL. Overall, patients had received a median of 2 prior systemic therapies (range, 1–8), and approximately one-third of patients were refractory to the last prior treatment. The investigators reported no differences in baseline characteristics between PTCL subtypes.

Overall, romidepsin was associated with a CR/CRu rate of 16% and an ORR of 28%. Response rates were similar between subgroups, although slightly lower in PTCL-NOS (Table 1). The investigators also reported on the disease control rate, defined as the proportion of patients with an objective response or stable disease for at least 90 days, as this outcome is meaningful due to the aggressive nature of PTCL. Overall, 46% of patients attained disease control with romidepsin. No differences in duration of response were noted according to baseline factors.

The median duration of response overall was 17 months. Among those with CR, the median duration of response was not reached except in patients with PTCL-NOS, in whom the median duration of response was 17 months. In the subgroup of patients

Table 1. Romidepsin in Relapsed or Refractory Peripheral T-Cell Lymphoma

	PTCL-NOS (n=69)	AITL (n=27)	ALK-1–negative ALCL (n=21)	Total (n=117)
Response rates, n (%)				
CR/CRu	10 (14)	5 (19)	4 (19)	19 (16)
ORR (CR/CRu + PR)	20 (29)	8 (30)	5 (24)	33 (28)
ORR + SD*	34 (49)	12 (44)	8 (38)	54 (46)

*Patients with stable disease for longer than 90 days.

AITL=angioimmunoblastic T-cell lymphoma; ALCL=anaplastic large cell lymphoma; CR/CRu=complete response/unconfirmed complete response; ORR=overall response rate; SD=stable disease; PR=partial response; PTCL-NOS=peripheral T-cell lymphoma not otherwise specified.

Data from Coiffier B et al. *Blood* (ASH Annual Meeting Abstracts). 2011;118. Abstract 591.

with AITL, the duration of response to romidepsin was not reached among all responders or among patients with a CR. PFS was better in AITL, both among responding patients and in the overall patient population. Most patients with responses to romidepsin had not responded to their most recent chemotherapy. Among the few who had responded to chemotherapy, the duration of response to chemotherapy was usually shorter than their duration of response to romidepsin.

The most common grade 3/4 adverse events were thrombocytopenia (25%), neutropenia (18%), infections (15%), anemia (9%), fatigue (7%), and leukopenia (5%). No differences were noted in the incidence of grade 3/4 adverse events across PTCL subtypes.

In conclusion, romidepsin is associated with durable responses in patients with relapsed PTCL, demonstrating similar response rates across the major PTCL subtypes. Some patients continue to respond more than 3 years after starting romidepsin. In this group of previously treated patients with an aggressive disease, nearly half of patients achieved disease control for at least 3 months. Toxicity was primarily hematologic and was similar across subtypes.

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Efficacy and Safety of Obinutuzumab (GA101) Monotherapy in Relapsed/Refractory Indolent Non-Hodgkin's Lymphoma: Results From a Phase I/II Study (BO20999)

Obinutuzumab (GA101) is a novel glycoengineered anti-CD20 monoclonal antibody. A type II antibody, obinutuzumab causes direct cytotoxic effects and enhances antibody-dependent cell-mediated cytotoxicity compared with type I CD20 antibodies, such as rituximab. Laboratory studies have shown that obinutuzumab binds to CD20 differently than type I antibodies.[1] Moreover, the glycosylation of obinutuzumab increases its availability to the Fc gamma receptors, enhancing antibody-dependent cell-mediated cytotoxicity. In vitro studies have demonstrated the superior antitumor activity of obinutuzumab compared with rituximab.[2,3]

Based on these preclinical findings, Salles and colleagues designed the phase I/II GAUGUIN (BO20999) study to evaluate the efficacy and safety of obinutuzumab in patients with relapsed or refractory indolent lymphoma. At ASH 2011, Salles and colleagues presented updated results from the study, with a median follow-up of 32 months for the phase I component and nearly 2 years for the phase II component.[4]

Phase I was a nonrandomized, dose-escalating study with obinutuzumab administered on Days 1 and 8 of Cycle 1 and Day 1 of Cycles 2–8 of 21-day cycles. Doses ranging from 50 mg to 2,000 mg were evaluated. Of the 16 patients with indolent lymphoma (13 with follicular lymphoma) in the phase I portion, the best ORR was 56%, including 31% CRs. No clear dose-response relationship was noted in the phase I portion of the study.

The phase II portion randomly assigned patients to 1 of 2 different obinutuzumab doses and schedules of administration. Patients in the first group received a flat dose of 400 mg obinutuzumab, using the same schedule as described previously. Patients in the second group received a 1,600-mg load-

ing dose at Day 1 and Day 8 of Cycle 1, and 800 mg thereafter. Of the 40 patients enrolled, 18 patients were assigned to the 400-mg group, and 22 patients were assigned to the 800-mg group.

The primary endpoint was end-of-treatment response, assessed 4 weeks after the last infusion. Most enrolled patients had stage III/IV follicular lymphoma and had received a median of 3 prior therapies (range, 1–11). All but 1 patient in each cohort had been previously exposed to rituximab, and approximately one-third of patients had failed a prior stem cell transplant. Approximately half of patients in both cohorts were refractory to rituximab, having had a lack of response or relapse within 6 months of their last rituximab administration.

In regard to safety, obinutuzumab was generally well tolerated. In the 400-mg cohort, grade 3/4 events were rare, and were limited to 1 case each of infection, pleural effusion, and renal failure. The incidence of grade 3/4 adverse events was slightly higher in the higher-dose cohort, but the major effects observed were 3 patients who presented with neutropenia and 4 patients who presented with infections. Grade 3/4 adverse events that were considered to be treatment-related were neutropenia in 3 patients, infusion-related reactions in 2 patients, and infection in 1 patient. Other adverse events were less common.

At the end of treatment, the ORR was 17% (3 of 18) in the 400-mg group (all partial responses) and 52% (12 of 23) in the 800-mg cohort, including 2 patients with a CR. The median duration of response was 17 months. The median PFS was 6 months in the 400-mg cohort and nearly 1 year in the 800-mg cohort. In the subset of rituximab-refractory patients, objective responses were observed in 1 patient in the 400-mg group and in 5 of 10 patients in the 800-mg cohort, including 1 CR. Further treatment upon relapse was permitted in patients initially attaining a response to GA101. A total of 5 patients received retreatment; 3 patients responded, although the data on duration of response are premature.

Allogeneic Transplant Following Brentuximab Vedotin Treatment in Patients With Relapsed or Refractory CD30+ Lymphomas

Illidge and colleagues presented a case series describing the initial experience with allogeneic SCT after brentuximab vedotin in patients enrolled in 1 of the 2 pivotal phase II trials of this agent (Abstract 3091). Of the 160 patients who participated in those 2 trials, 15 patients (9%) received an allogeneic stem cell transplant as their first subsequent therapy; this included 7 patients with Hodgkin lymphoma and 8 patients with systemic ALCL. The median age of these patients was 28 years (range, 17–61 years), 67% were female, and the median time since lymphoma diagnosis was 27 months (range, 6–108 months). Patients had received a median of 3 therapies prior to brentuximab vedotin (range, 2–5), and 12 of 15 patients had received a prior autologous SCT. Patients had received a median of 9 cycles of brentuximab vedotin (range, 4–16) in the phase II trials. All patients had an objective response to brentuximab vedotin, with the best response a CR for 12 patients and a PR for 3 patients. The median time to response was 1.4 months, and all patients still had an objective response at the last assessment before allogeneic SCT. The median interval between the last dose of brentuximab vedotin and the start of the SCT conditioning regimen was 1.4 months (range, 0.6–3.3 months). After a median follow-up of 16.9 months from the first dose of brentuximab vedotin, the median PFS was 21.1 months. At the time of analysis, 10 patients (67%) remained in remission, and 5 patients had progressed or died post-transplant, including 1 patient with Hodgkin lymphoma and 4 patients with systemic ALCL. Two of these patients died; both had a systemic ALCL with a CR after brentuximab vedotin. One death was disease-related and the other was attributed to transplant-related complications. The median PFS was 21.1 months. Treatment-related adverse events that developed prior to allogeneic SCT in more than 30% of patients included peripheral sensory neuropathy (53%), pyrexia (53%), diarrhea (47%), neutropenia (47%), and nausea (33%). Grade 3 or higher adverse events developed in 87% of patients. The most common grade 3 or higher adverse events were neutropenia (47%), anemia (27%), and thrombocytopenia (27%). Two patients discontinued brentuximab vedotin prior to allogeneic SCT due to peripheral sensory neuropathy. The investigators suggested that additional studies were warranted to further explore the use of brentuximab vedotin to enable consolidative allogeneic SCT.

The investigators concluded that this first-in-human study demonstrated clear activity with obinutuzumab in patients with relapsed or refractory lymphoma, including rituximab-refractory patients. Obinutuzumab was associated with an acceptable safety profile, with few grade 3/4 events. A flat 1,000-mg dose has been selected for further study. Obinutuzumab is now being evaluated in phase III trials.

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Current and Emerging Therapies for Peripheral T-Cell Lymphomas

In an education session, Dr. Kerry Savage reviewed current and emerging therapies for PTCL.[1] She noted that the classification of T-cell lymphomas has evolved dramatically as a better understanding has emerged of the clinical and pathologic features associated with different types of PTCLs. In 2008, the World Health Organization updated the PTCL classification scheme, adding further complexity. The most common PTCL subtypes found in North America are PTCL-NOS, AITL, and systemic ALCL (Figure 4).[2]

Today, cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy remains the standard therapy for PTCL. This recommendation evolved from the large, randomized Southwest Oncology Group trial which showed that, in patients with advanced NHL, CHOP was as effective as intensive second-generation and third-generation CHOP-like regimens, but less toxic.[3] However, this trial was performed before the routine use of immunophenotyping, and the effect of intensive regimens in the context of greater diagnostic information is unknown. Moreover, this treatment standard is based on data primarily in diffuse large B-cell lymphoma (DLBCL). However, outcomes in PTCL are worse than those in DLBCL. Moreover, within the broad category of PTCL, there is significant heterogeneity in outcomes across subtypes. One subtype with particularly favorable outcomes is ALK-positive ALCL; outcomes in other subtypes are significantly worse.[2] However, even in patients with ALK-positive ALCL, outcomes vary according to IPI risk factors, demonstrating the importance of both biologic and clinical factors.[4]

CHOP is associated with 5-year failure-free survival rates of 20–36% across PTCL subtypes.[2] It has been hypothesized that PTCL has an inherent resistance to anthracyclines. An analysis of patients with PTCL-NOS showed no difference in outcomes in patients receiving anthracycline-containing regimens versus those receiving non–anthracycline-based regimens.

Although it is unclear whether CHOP is the optimal regimen for the heterogeneous diseases comprising PTCL, there is no clear alternative. Given the infrequency of the disease, there are few randomized, controlled trials. Schmitz and colleagues conducted a retrospective analysis evaluating the role of etoposide in the treatment of PTCL in 343 patients treated in trials of the German High-Grade Non-Hodgkin Lymphoma Study Group.[5] In older patients, there was no benefit with etoposide. However, among younger, favorable-risk patients, the addition of etoposide to CHOP (CHOEP) was associated with a significant improvement in 3-year event-free survival (75.4% vs 51.0% for CHOP alone [P=.003]) but no difference in overall survival. Therefore, although etoposide may be important in PTCL, additional studies are needed.

Dose intensity requiring repeated stem cell transplantation was also evaluated as an approach to improve efficacy

Fludarabine and Mitoxantrone Followed by Yttrium-90 Ibritumomab Tiuxetan in Untreated Patients With Follicular Lymphoma. Long-Term Efficacy and Toxicity Results of the FLUMIZ Trial

Zinzani and colleagues presented long-term efficacy and toxicity results from the multicenter, nonrandomized, phase II FLUMIZ trial of fludarabine and mitoxantrone followed by yttrium-90 ibritumomab tiuxetan in patients with previously untreated follicular NHL (Abstract 1604). Between June 2004 and April 2006, the study enrolled 61 patients with stage III and IV follicular lymphoma at 13 Italian centers. The treatment consisted of oral fludarabine 40 mg/m^2 on Days 1–3, intravenous mitoxantrone 10 mg/m^2 on Day 1 every 28 days for 6 cycles, followed by 1 course of 90Y-labeled ibritumomab tiuxetan. Radioimmunotherapy included 2 weekly infusions of rituximab 250 mg/m^2 followed by weight-based dosing of yttrium-90 ibritumumab tiuxetan. Of the 61 patients who enrolled, 57 patients completed the 6 cycles of chemotherapy and received radioimmunotherapy. The remaining patients were excluded due to disease progression (1 patient) and bone marrow infiltration greater than 25% (3 patients) after completing chemotherapy. After a median follow-up of 52 months, the 5-year PFS rate was 68%, and the estimated 5-year OS rate was 93%. The investigators reported no late hematologic side effects. After more than 4 years of follow-up, 22 patients (38%) were in first complete remission, and 16 patients (28%) had relapsed; 4 patients (7%) had died due to relapse. All patients with relapsed disease received second-line chemotherapy, which included high-dose chemotherapy with stem cell rescue in 4 patients. The investigators concluded that these long-term results compare favorably with those observed with chemoimmunotherapy alone, without increasing the risk of secondary hematologic malignancies.

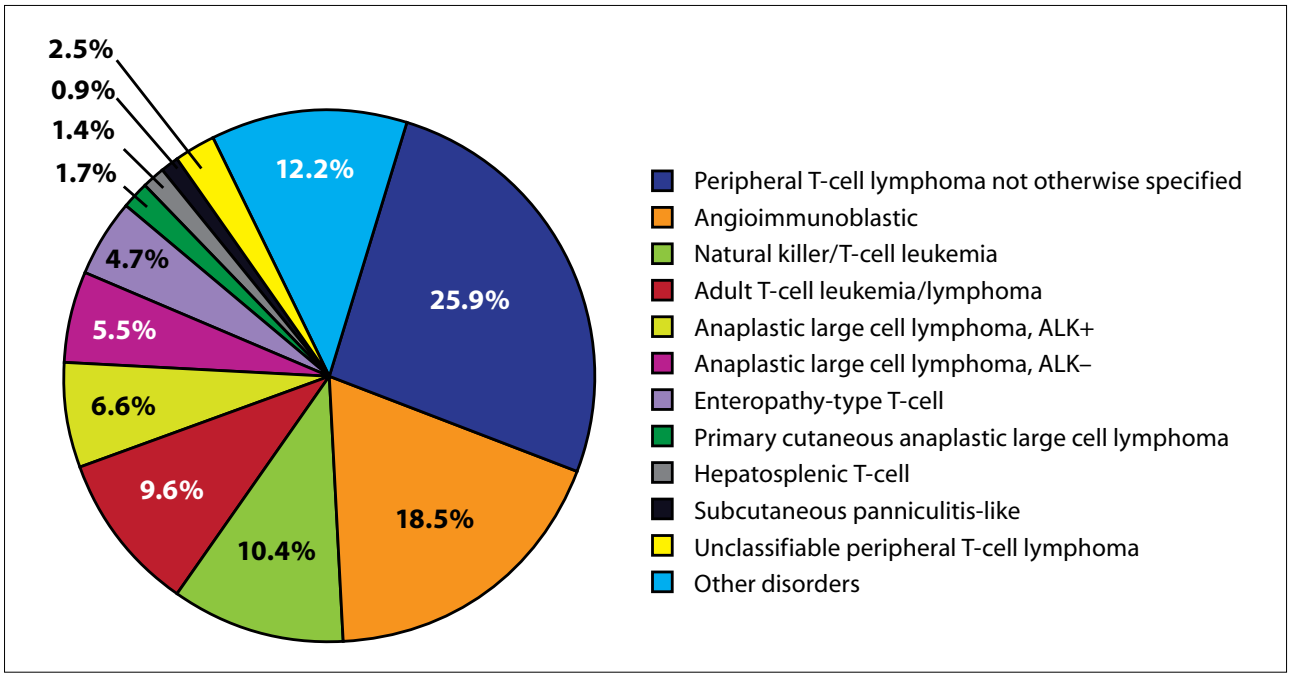

Figure 4. Subtypes of peripheral T-cell lymphoma identified in the International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study. ALK=anaplastic lymphoma kinase. Adapted from the International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study: pathology findings and clinical outcomes. *J Clin Oncol.* 2008;26:4124-4130.

in patients receiving CHOP plus etoposide. However, there was a trend toward worse outcomes in patients treated with the dose-intensive approach with stem cell transplantation. The role of stem cell transplant in patients in first remission in PTCL remains hotly debated. No randomized, controlled studies have evaluated the role of ASCT in PTCL, and there are data supporting both sides of the issue. It may be that certain PTCL subtypes may preferentially benefit from ASCT. The Nordic Lymphoma Group first-line transplant study evaluated the role of ASCT in patients with previously untreated PTCL. The study enrolled 160 patients age 67 or younger with confirmed systemic ALK-negative PTCL. Patients received 6 cycles of CHOEP administered every 14 days (CHOEP-14) or CHOP-14 in patients older than age 60. Patients attaining at least a PR went on to receive high-dose chemotherapy and stem cell transplantation. For the overall cohort, the 5-year OS and PFS rates were 51% and 44%, respectively.[6] Perhaps, therefore, PTCL therapy should be tailored based on disease heterogeneity. For example, anthracycline-based chemotherapy appears to be effective in most patients with ALK-positive ALCL. Evidence suggests that extranodal natural killer (NK)/T-cell lymphoma may be better managed with a different approach. In advanced-stage extranodal NK/T-cell disease, L-asparaginase–based combination chemotherapy appears to be active. In a phase II study of 38 patients with newly diagnosed stage IV, relapsed or refractory extranodal NK/T-cell lymphoma, the SMILE chemotherapy regimen of dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide was associated with an ORR of 79% after 2 cycles and a 1-year OS rate of 55%.[7] The SMILE regimen is associated with significant toxicity, with 92% of patients developing grade 4 neutropenia and 61% of patients developing grade 3/4 infections. Longer follow-up is needed to gain a better understanding of the efficacy and safety of this approach.

Novel approaches are being investigated in both the first-line treatment of PTCL and for patients with relapsed or refractory disease. Gemcitabine has been evaluated both as a single agent and as part of a combination regimen. Several studies have evaluated the addition of other agents to CHOP chemotherapy. A widely studied approach has been the addition of the monoclonal antibody alemtuzumab to CHOP chemotherapy. Alemtuzumab binds to CD52, an antigen present on most normal and malignant B cells and T cells. Because alemtuzumab also targets almost all immune cells, it is associated with significant immunosuppression. Moreover, CD52 expression is more heterogeneous in PTCLs than in B-cell lymphomas. Multiple phase II studies have evaluated CHOP plus alemtuzumab administered using a variety of schedules and doses. The Dutch-Belgian Hemato-Oncology Group (HOVON) evaluated an intensive approach of 8 cycles of CHOP plus 90 mg of alemtuzumab per cycle.[8] The ORR was 90%, although relapses were common; the median OS and event-free survival were 27 months and 10 months, respectively. Toxicity is a significant concern with this approach. In the HOVON study, 8 patients (40%) developed neu-

Prolonged Treatment With Brentuximab Vedotin (SGN-35) in Patients With Relapsed or Refractory Hodgkin Lymphoma (HL) or Systemic Anaplastic Large Cell Lymphoma (sALCL)

Patients enrolled in the pivotal trials of brentuximab vedotin in relapsed/refractory Hodgkin lymphoma or systemic ALCL could receive up to 16 cycles of treatment. The median number of cycles administered to patients with Hodgkin lymphoma and systemic ALCL was 10 and 7, respectively. At ASH 2011, Forero-Torres and colleagues presented a retrospective analysis of outcomes in a subset of patients who received more than 16 cycles in a treatment-extension study (Abstract 3711). In the extension study, brentuximab vedotin was continued until disease progression, unacceptable toxicity, or withdrawal of consent. Among the 17 patients who received more than 16 consecutive cycles of brentuximab vedotin, the median duration of treatment was 17.3 months. The overall objective response rate was 88%, which included 76% CR and 12% PR. The median time to objective response was 2.5 months. The median duration of objective response had not been reached (the range was from 8.3 months to >23.2 months). The most common adverse events were peripheral sensory neuropathy (71%), upper respiratory tract infection (53%), and fatigue (47%). Other events included cough, alopecia, diarrhea, neutropenia, and pyrexia.

tropenic fever and 7 patients (35%) had cytomegalovirus (CMV) reactivation, 1 with CMV disease.[8] Moreover, 3 patients (15%) developed Epstein Barr virus–related lymphoma. The ongoing ACT I and ACT II (Alemtuzumab and CHOP in T-Cell Lymphoma) studies are evaluating the role of alemtuzumab in younger patients and in older patients.

Denileukin diftitox is also being evaluated as an addition to CHOP in patients with PTCL. In a phase II study of 49 patients, denileukin diftitox plus CHOP was associated with an ORR of 65% (51% CR) and an estimated 2-year OS of 60%.[9] A phase III study evaluating this approach is planned.

Treatment options for patients with relapsed or refractory PTCL have been evolving rapidly, with 3 new drugs approved by the FDA in the past 2 years. The first new drug to be approved was the novel antifolate pralatrexate. In the phase II Pralatrexate in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma (PROPEL) study, which enrolled 115 patients with relapsed or refractory PTCL, pralatrexate was associated with an ORR of 29%, including 11% CR.[10] The median duration of response was 10.1 months, and the median PFS and OS were 3.5 and 14.5 months, respectively. Several studies are now evaluating pralatrexate in patients with previously untreated PTCL, both as a component of initial therapy and as maintenance therapy after CHOP chemotherapy.

The second agent recently approved in PTCL is the HDAC inhibitor romidepsin. The pivotal trial of romidepsin in relapsed/refractory PTCL was a single-arm study in 131 patients with PTCL who had failed at least 1 prior systemic therapy.[11] In this study, romidepsin was associated with an ORR of 26% (13% CR) and a median duration of response of 12 months. The most common toxicities were hematologic adverse events, nausea, and vomiting. Romidepsin appears to provide durable responses, particularly in patients with AITL, in whom the median duration of response has not been reached but was ongoing at 34 months.[12] Romidepsin is now being evaluated in the frontline setting in combination with CHOP.[13]

The third drug to recently gain FDA approval is brentuximab vedotin, which is now approved for use in patients with systemic ALCL. In a phase II study, brentuximab vedotin was associated with an ORR of 86% and complete remission rate of 57%, in a group of previously treated patients, including 26% who had failed ASCT.[14] The primary toxicity associated with brentuximab vedotin is peripheral neuropathy, which is largely reversible. Brentuximab vedotin is also being evaluated in the first-line setting, in combination with CHOP as the primary therapy in patients with systemic ALCL.

Other compounds with varying mechanisms of action are also being evaluated in PTCL, including the alkylating agent bendamustine, the aurora A kinase inhibitor alisertib, and the immunomodulatory agent lenalidomide. As the treatment of PTCL continues to evolve, treatments that are tailored for specific subtypes will likely play a role in the future. However, given the rarity of PTCL, participation in clinical trials and collaboration between institutions will be essential for progress.

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Preclinical Activity of Brentuximab Vedotin (SGN-35) in Primary Effusion Lymphoma (PEL)

Primary effusion lymphoma (PEL) is an aggressive NHL subtype characterized by pleural, peritoneal, or pericardial malignant effusions, often without a tumor mass. PEL is found in individuals with immunosuppression, most often in those with HIV infection. The median survival with current therapies is 6 months. Based on previous reports of CD30 expression in PEL cells, Bhatt and colleagues conducted additional studies investigating the expression of CD30 expression on PEL cells and the preclinical activity of brentuximab vedotin in PEL (Abstract 3728). The researchers first reviewed immunohistochemical and flow cytometric results indicating CD30 expression in patients diagnosed with PEL at the University of Miami. They then demonstrated CD30 expression in PEL cell lines by flow cytometry. Treatment of multiple PEL cell lines with brentuximab vedotin was associated with significant cytotoxicity. Cell proliferation was reduced at 48 hours and was completely arrested at 72 hours. Apoptosis and cell death of brentuximab vedotin–exposed cells was also evident at 72 hours post-treatment. MMAE conjugated to nonspecific IgG was not cytotoxic, confirming the specificity of the CD30-conjugated drug. Cells exposed to brentuximab vedotin demonstrated cell cycle arrest at the G2/M phase prior to apoptosis. RNA analysis showed that brentuximab vedotin did not affect the KSHV viral gene in a PEL cell line. Finally, the investigators demonstrated activity of brentuximab vedotin in a murine xenograft model, in which brentuximab vedotin extended the survival of mice exposed to PEL cells. Together, these findings provide support for clinical evaluations of brentuximab vedotin in patients with PEL.

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Commentary

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There were many important presentations on lymphoma at the 2011 American Society of Hematology (ASH) meeting. Clinical trials provided new data on agents such as brentuximab vedotin, obinutuzumab, and romidepsin, as well as on the use of radioimmunotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).

Brentuximab Vedotin

Several clinical studies examined the use of brentuximab vedotin (Adcetris). I presented results from a phase I trial of brentuximab vedotin with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) or doxorubicin, vinblastine, and dacarbazine (AVD) in patients with newly diagnosed advanced-stage Hodgkin lymphoma,[1] which was built on the pivotal phase II study by Chen and colleagues[2] that led to the drug's approval. In the previous study, brentuximab vedotin was shown to have single-agent activity in heavily pretreated patients who had relapsed after autologous transplant. The overall response rate was approximately 75%, and the complete response (CR) rate was approximately 34%.[2] When a drug has very good single-agent activity in the relapse setting, it makes sense to move it upfront, and then combine it with a preexisting therapy that has activity but does not cure all patients. It is hoped that the addition of a new active agent will improve the cure rate. This objective was the background behind the combination regimen used in the study I presented.[1] This study was a classic phase I trial that incorporated a new drug and dose escalation, with a fixed dosing schedule of the standard regimen, in this case, ABVD. The trial started with an initial cohort, which received the standard ABVD, and subsequently moved to a second cohort, which received AVD (without the bleomycin). The rationale behind this approach was that the addition of brentuximab vedotin, with its impressive single-agent activity, would eliminate the need for bleomycin, which does not

have impressive single-agent activity[3] and is a weaker drug in terms of activity. In addition, it is associated with lung toxicity,[4] an unpredictable event that can cause shortness of breath, cough, and, in rare instances, death.

The trial showed that it is possible to combine AVD with brentuximab vedotin, with minimal toxicity.[1] When brentuximab vedotin was added to ABVD, there was an increase in what appeared to be bleomycin-associated lung toxicity, at a higher incidence than has been seen with AVD alone. The conclusion from this trial is that AVD plus brentuximab vedotin was safe. This is a phase I trial, and we need to complete treating patients in this cohort to take a snapshot of the activity of this regimen. At the time this trial was presented at ASH, all patients achieved complete remission, and more than 90% achieved PET negative status after 2 cycles of ABVD, suggesting that this combination may be very effective. A randomized trial planned for 2012 will compare standard ABVD with the new regimen, which will be AVD plus brentuximab vedotin.

Chen presented results from a study examining the use of brentuximab vedotin in patients undergoing allogeneic hematopoietic cell transplantation in relapsed/refractory Hodgkin lymphoma.[5] When patients relapse from autologous transplant, they usually have a very poor overall survival of approximately 2.5 years. The median age of these patients is in the 30s, and it is devastating for them to learn that they have such a short time left to live. Clearly this group of patients represented an unmet medical need, which helped facilitate the accelerated approval of brentuximab vedotin. The question is, now that we are seeing very good activity with brentuximab vedotin in this patient setting, how can we build on this success? There are several strategies. One is to offer allogeneic transplant to patients who achieve complete remission with brentuximab vedotin, to see if overall survival and event-free survival can be prolonged. In the study presented by Chen,[5] this approach was safe, and the majority of patients remained in remission after receiving allogeneic transplant. These results are very encouraging. We know that the majority of patients who achieve complete remission with brentuximab vedotin will remain in complete remission for 2 years or longer. The question is: Should all patients who achieve complete remission be offered allogeneic transplant automatically? Or should allogeneic transplant be reserved for patients who are very likely to relapse even after they achieve complete remission, knowing that allogeneic transplant is associated with toxicity and mortality? Although a randomized trial could help resolve this issue, it would be difficult to randomize patients to one arm that includes allogeneic transplant and one arm that does not. Ultimately, we will have to depend on risk stratification. This trial has paved the way for similar studies.

Advani presented follow-up data for a phase II study of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma.[6] Earlier results from this study, presented at the 2010 ASH meeting[7] and the 2011 American Society of Clinical Oncology meeting,[8] showed that brentuximab vedotin was highly effective in relapsed anaplastic large cell lymphomas, with a response rate of more than 80% and a complete response rate of approximately 50%, in both ALK-positive patients and ALK-negative patients (who traditionally have a worse prognosis.) The follow-up data show that there is extended benefit in terms of event-free survival for these patients. This finding is the basis for an ongoing phase I trial in the frontline setting, which is evaluating brentuximab vedotin plus CHOP, with and without vincristine,[9] because of the overlapping neurotoxicity between vincristine and brentuximab vedotin.

A study presented by Illidge[10] examined data on allogeneic stem cell transplant after brentuximab vedotin from studies by Chen[5] and Pro.[8] Patients in these studies (N=160) had received a median of 9 cycles of brentuximab vedotin. All patients had an objective response to brentuximab vedotin; 12 achieved a complete response and 3 achieved a partial response. The median progression-free survival was approximately 21 months from the first dose of brentuximab vedotin.

Forero-Torres and colleagues performed a retrospective analysis of patients who received more than 16 cycles of brentuximab vedotin in previous studies.[11] Among the 17 patients, the overall objective response rate was 88%. The median progression-free survival and median duration of response had not been reached. Brentuximab vedotin was well tolerated.

Obinutuzumab

The introduction of rituximab into the management of B-cell lymphoma has revolutionized the treatment approach to this disease. Yet, many lymphomas fail to respond to rituximab or relapse after an initial response. Several mechanisms have been proposed to explain the shortcomings of rituximab, including possible internalization of the rituximab-CD20 complex and FCγIIR polymorphism. New anti-CD20 antibodies that are more effective than rituximab are, therefore, highly needed. Obinutuzumab (GA101) is the only type II glycoengineered, humanized anti-CD20 monoclonal antibody in clinical development for the treatment of lymphoma and chronic lymphocytic leukemia. Salles and colleagues reported the results of a phase I/II study in patients with relapsed/refractory indolent non-Hodgkin lymphoma.[12] All patients received prior rituximab therapy, and some patients were refractory to rituximab. Two dose levels were tested in the phase II part, with the more intensive dose producing a 60% response rate in 20 patients. These encouraging data led to the design of a randomized phase II trial comparing the efficacy and safety of GA101 (1,000 mg) with rituximab (375 mg/m^2). Both drugs were administered weekly

for 4 weeks in patients with relapsed indolent NHL. Sehn and coworkers presented preliminary results of this study, which demonstrated a higher efficacy of obinutuzumab compared with rituximab (overall response rate 42% vs 24%, respectively).[13] This is the first head-to-head trial of GA101 against rituximab, which demonstrated higher response rates with a similar safety profile. Although these results are very encouraging, it will be important to demonstrate that this improved efficacy is maintained when GA101 is combined with chemotherapy. In fact, this question will be answered in randomized phase III trials in combination with chemotherapy in the near future.

Romidepsin

Coiffier provided follow-up data from the pivotal romidepsin study in relapsed or refractory T-cell lymphoma.[14] In the initial report, the overall response rate in 130 patients was 25% (with 15% CR/unconfirmed CR).[15] With more than 20 distinctive subtypes of PTCL, clinicians wondered whether romidepsin is more or less effective in specific subsets. This answer could be addressed in the 3 major subtypes of PTCL: PTCL not otherwise specified (NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic lymphoma kinase-1–negative anaplastic large cell lymphoma (ALK-1–negative ALCL). It was reassuring that the overall response rate was similar across these 3 major subtypes, including 30% in patients with AITL. With a median duration of follow-up of 10.9 months, the median duration of response for all responders was 17 months for patients with PTCL-NOS and 12 months for patients with ALK-1–negative ALCL. The results confirmed that there is a subset of patients who would benefit from this histone deacetylase inhibitor, which is a step forward for the treatment of patients with PTCL. However, future directions should focus on combining romidepsin with other active agents to improve the outcome of frontline regimens.

CHOP Plus Radioimmunotherapy

Press presented results from a phase III trial of CHOP plus rituximab versus CHOP plus iodine-131-tositumomab for the newly diagnosed follicular non-Hodgkin lymphoma (SWOG S0016).[16] This trial was very important because it was hoped that CHOP plus radioimmunotherapy would be more effective than CHOP plus rituximab, the current standard regimen. However, the trial showed that there was no benefit to this approach. This outcome is disappointing because the CHOP plus radioimmunotherapy regimen is simpler. It is just 1 course—8 days—of the radioimmunotherapy. There was no maintenance in either arm of this trial.

It is probable that these data will negatively impact the entire field of radioimmunotherapy for patients with indolent lymphomas. The 2 radioimmunotherapy products approved by the FDA, tositumomab and ibritumomab tiuxetan, show very impressive single-agent activity; each one has a response rate of approximately 70% in rituximab-refractory patients.[17,18] So far, however, these agents have failed to show survival advantages in any trials. This trial adds to the negative impression. As of today, rituximab plus CHOP, with or without maintenance rituximab, remains the standard of care for these patients.

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