

**A SPECIAL MEETING REVIEW EDITION**

**Highlights in Lymphoma From the 2012 European Hematology Association Annual Meeting**

June 14–17, 2012 · Amsterdam, The Netherlands

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**Special Reporting on:**

- The Microenvironment in Classical Hodgkin Lymphoma Shows Evidence of a TH1 and Not TH2 Response With TBET Expression Being Associated With Improved Survival and EBV Status
- Comparing Intensity of Chemotherapy Followed by PET-Guided Radiotherapy in Patients With Advanced Stage Hodgkin Lymphoma: Final Results of the GHSG HD15 Trial
- Long-Term Follow-Up Results of an Ongoing Pivotal Study of Brentuximab Vedotin in Patients With Relapsed or Refractory Hodgkin Lymphoma (HL)
- Outcome of Patients With Early Stage Hodgkin Lymphoma According to GHSG and NCIC-CTG Risk Classification: The Princess Margaret Hospital Experience
- Treatment-Related Mortality in Patients Undergoing Therapy for Advanced Hodgkin's Lymphoma: Analysis of the German Hodgkin Study Group (GHSG)

**PLUS Meeting Abstract Summaries**

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# CD30-directed therapy

## Important Safety Information

### BOXED WARNING

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

### Contraindication:

Concomitant use of ADCETRIS and bleomycin is contraindicated due to pulmonary toxicity.

### Warnings and Precautions:

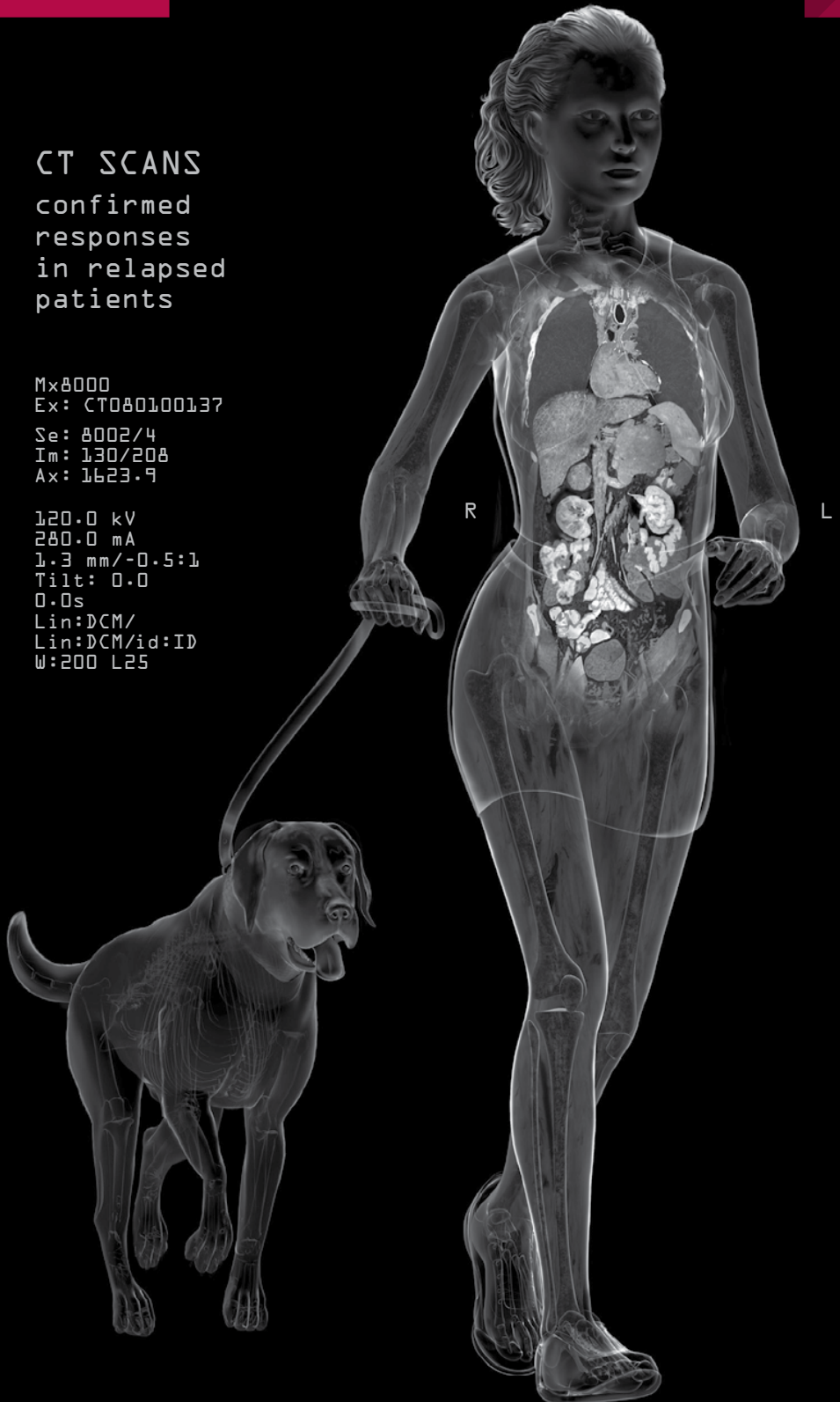
- **Peripheral neuropathy:** ADCETRIS treatment causes a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. ADCETRIS-induced peripheral neuropathy is cumulative. Treating physicians should monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness and institute dose modifications accordingly.
- **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.
- **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 ( $\geq 1$  week) severe neutropenia can occur with ADCETRIS.
- **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.

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# After multiple failures, single-agent response

## Indicated for the treatment of:

- Hodgkin lymphoma (HL) after failure of autologous stem cell transplant (ASCT)<sup>1</sup>
- HL in patients who are not ASCT candidates after failure of at least 2 multiagent chemotherapy regimens<sup>1</sup>

**HL: 73%** objective response rate (ORR) (95% CI: 65%-83%)<sup>1</sup>

**32%**  
complete remission  
(95% CI: 23%-42%)<sup>1</sup>

**40%**  
partial remission  
(95% CI: 32%-49%)<sup>1</sup>

N = 102, 15-77 years (median: 31 years)<sup>1</sup>

- Systemic anaplastic large cell lymphoma (sALCL) after failure of at least 1 multiagent chemotherapy regimen<sup>1</sup>

**sALCL: 86%** ORR (95% CI: 77%-95%)<sup>1</sup>

**57%**  
complete remission  
(95% CI: 44%-70%)<sup>1</sup>

**29%**  
partial remission  
(95% CI: 18%-41%)<sup>1</sup>

N = 58, 14-76 years (median: 52 years)<sup>1</sup>

The indications for ADCETRIS™ (brentuximab vedotin) are based on response rate. There are no data available demonstrating improvement in patient-reported outcomes or survival with ADCETRIS.<sup>1</sup>

## Important Safety Information (continued)

- **Progressive multifocal leukoencephalopathy (PML):** JC virus infection resulting in PML and death has been reported in ADCETRIS™ (brentuximab vedotin)-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.
- **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:** Fetal harm can occur. Pregnant women should be advised 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 (≥20%), regardless of causality, were neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough and vomiting.

## Drug Interactions:

Patients who are receiving strong CYP3A4 inhibitors concomitantly with ADCETRIS should be closely monitored for adverse reactions.

 CD30-DIRECTED  
**ADCETRIS™**  
brentuximab vedotin

**Please see Brief Summary of full Prescribing Information, including Boxed WARNING, on the last page of this ad.**

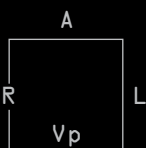
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CD30-DIRECTED  
**ADCETRIS**<sup>™</sup>  
brentuximab vedotin

### 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<sup>™</sup> (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 ( $\geq 1$  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 ( $\geq 10\%$ ), 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, pruritus, 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 ( $\geq 20\%$ ), regardless of causality, were neutropenia, peripheral sensory neuropathy, fatigue, upper respiratory tract infection, nausea, diarrhea, anemia, pyrexia, thrombocytopenia, rash, abdominal pain, cough, and vomiting. The most common serious adverse reactions experienced by HL include peripheral motor neuropathy (4%), abdominal pain (3%), pulmonary embolism (2%), pneumonitis (2%), pneumothorax (2%), pyelonephritis (2%), and pyrexia (2%).

ADCETRIS<sup>™</sup> (brentuximab vedotin) 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 ( $\geq 20\%$ ), 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 ( $\geq 99\%$ ), 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 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.



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## The Microenvironment in Classical Hodgkin Lymphoma Shows Evidence of a TH1 and Not TH2 Response With TBET Expression Being Associated With Improved Survival and EBV Status

Classical Hodgkin lymphoma (CHL) is a heterogeneous malignancy with a complex etiology and epidemiology. It occurs in both young and elderly patients and is typically curable by chemotherapy and radiotherapy. However, challenges remain in the 10–20% of patients who continue to relapse or progress. Immunotherapeutic and allogeneic transplantation strategies are known to be unsuccessful in this subset of patients, and no new treatment strategies have emerged.

CHL is pathologically unique in that the bulk of the tumor is not malignant B cells, but an immune infiltrate dominated by CD4+ T cells and macrophages. This microenvironment has a heterogeneous composition in most patients, and it may provide biomarkers to help identify the subset of patients who will suffer unnecessary late effects. Approximately 20–30% of CHL patients also have Epstein-Barr virus (EBV).

Although the histology of the disease is familiar, the malignant cell represents a very small component of the microenvironment. The microenvironment is otherwise comprised of macrophages in a city of lymphocytes that are mainly T cells. Questions remain as to whether or not these T cells and their composition are of prognostic relevance, if the identified markers on these T cells can discriminate patients, why the T cells do not perform their function of removing the tumor, and if that is due to a TH2 bias or to an infiltration of regulatory T cells (Treg). Furthermore, if the molecular mechanisms were better understood, could they be modulated?

### ABSTRACT SUMMARY Randomized Phase II Trial Comparing Obinutuzumab (GA101) With Rituximab in Patients With Relapsed CD20+ Indolent B-Cell Non-Hodgkin Lymphoma: Preliminary Analysis of the GAUSS Study

GA101 (obinutuzumab) is a glycoengineered type II anti-CD20 monoclonal antibody that had higher favorable response rates and no appreciable differences in safety compared with rituximab in this phase II trial of patients with relapsed indolent non-Hodgkin lymphoma (NHL).

The trial enrolled 175 patients (149 with follicular lymphoma and 26 with non-follicular indolent NHL) who had relapsed CD20+ indolent NHL that required therapy and had demonstrated a prior response to a rituximab-containing regimen lasting at least 6 months (Abstract 0790). The patients were randomized 1:1 to receive 4 weekly infusions of either GA101 or rituximab, and their end-of-treatment responses were assessed 28–42 days after their last induction dose. Those patients who did not have evidence of progression after induction therapy continued to receive maintenance GA101 or rituximab for up to 2 years at the same dose.

Investigator assessment of ORR found that the GA101 arm had a higher ORR (44.6%) than the rituximab arm (33.3%; difference of 11.3%, 95% CI, -5.1–27.6;  $P=.08$ ). When a blinded independent review facility also assessed responses, GA101 again had a higher ORR (44.6%) than rituximab (26.7%; difference of 17.9%; 95% CI, 2.0–33.8;  $P=.01$ ). With a median observation time of 15 months, the median PFS was the same in both arms.

GA101 had higher rates of infusion-related reactions (any grade, 74% vs 51%) than rituximab, and higher rates of cough (21% vs 6%). Most of these adverse events were grade 1 or 2 in severity and did not result in significant differences in treatment discontinuation. Other common adverse events were fatigue (25% with GA101 vs 20% with rituximab) and upper respiratory tract infection (8% vs 10%). GA101 combined with chemotherapy is now in phase III trials.

The importance of a lymphocyte infiltrate as it relates to cancer in general has been recognized for some time, and it may confirm prognostic outcomes. The nature of this infiltrate is important. A key component of the lymphoid infiltrate is the regulation

of the T cell, which is physiologically responsible for suppressing aberrant immune responses. The Treg marker FOXP3 has been used to probe the microenvironment and to determine if FOXP3 has prognostic significance. Functional evidence suggests that a

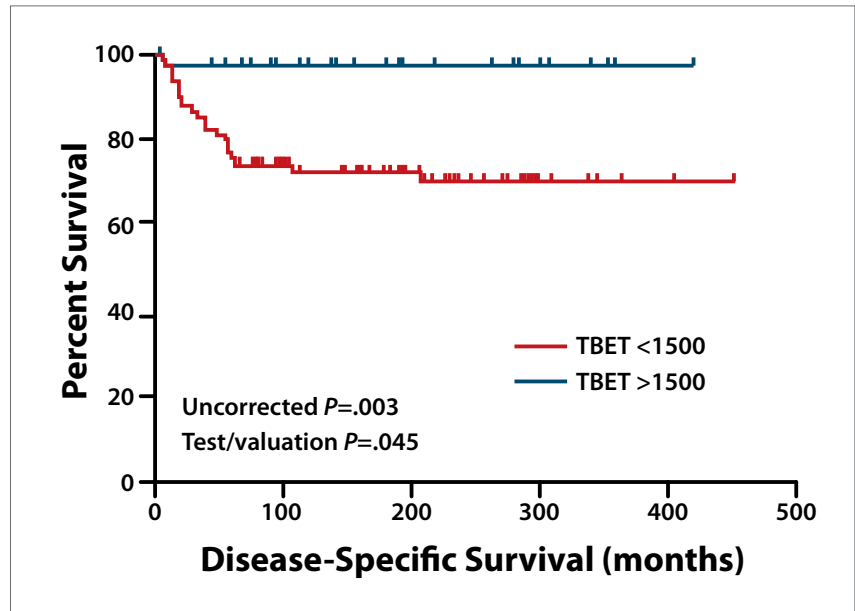


regulator of a T cell might suppress tumor immunity and thus, intuitively, a higher infiltrate would be associated with a poorer prognosis. While the prognostic significance of FOXP3 has been studied in solid tumors, only controversial evidence exists in lymphoid malignancies. Many researchers have shown that FOXP3 expression in microenvironments is associated with superior outcomes, despite the uncertainty of the mechanism.<sup>1</sup> FOXP3 may interact with macrophages and other important components to confirm a prognostic signature. However, no functional evidence about FOXP3 exists in CHL.

Some immunohistochemistry evidence suggests that the TH1 or TH2 bias of the microenvironment may be associated with prognosis.<sup>2</sup> The microenvironment may have a TH2 bias, which might suppress a successful TH1-mediated immune response, but the data are early, not functional, and limited to immunohistochemistry. Regulated T cells may be involved, and complex interactions with EBV may affect TH1 and TH2 bias.

Paul Greaves, MD, and colleagues sought to use tissue microarray immunohistochemistry with tissue derived from patients treated at Barts Cancer Institute.<sup>3</sup> The goals were to determine the heterogeneity of T cell subsets, find transcription factors, and determine whether prognosis was impacted by FOXP3 and EBV status. They sought to validate the findings with transcription factors through cytokine assays that could show the functional infiltrate of TH1 versus TH2.

Strict quality controls for the tissue microarray procedure ensured the pairability of samples. Because CHL is so heterogeneous, preparing samples is difficult. A highly cellular infiltrate comprising many malignant cells without extensive areas of fibrosis is needed. Thus, tissue microarrays were performed in triplicate for each patient and stained for TBET (for TH1), GATA3 (for TH2), and CMAF (for TH2). All analyses used automated



**Figure 1.** Disease-specific survival (DSS) by number of TBET+ cells.

Data from Greaves P et al. Paper presented at: 17th Congress of the European Hematology Association; Abstract 1107.

image analysis to enable large areas of tumor assessment and many events to be counted while avoiding observer fatigue and maintaining good inter-observer validity. Counts of cells were expressed as total numbers per 1 mm<sup>2</sup>, and patient groups were discriminated by cutpoints based on the numbers of cells expressing each marker using a test/validation set methodology.

Formalin-fixed, paraffin-embedded tissue was available for 122 patients who had a very long median follow-up of 16 years (range, 2–40 years). The tissue samples were relatively enriched for advanced-stage patients, possibly reflecting the increased availability of tissue from advanced-stage patients. The median age of the patients was 30 years, 65% were male, and 71% had advanced stage disease.

T cells were defined with antibodies to CD3, CD4, and CD8. Wide heterogeneity was clear. GATA3, a marker of TH2, is the defining transcription factor for TH2. GATA3 suppresses TH1 responses and polarizes cells with the TH2 phenotype. GATA3 was nota-

bly absent in the microenvironment for the vast majority of cases, which is not novel, but a widely demonstrated finding. Notably, TH1 was highly expressed in the majority of cases. The expression of TH1 was heterogeneous across the cases.

When TBET was compared with FOXP3, which is of known prognostic significance, TBET had less expression overall than FOXP3. A possible, slight correlation may associate TBET with FOXP3.

Interestingly, expression of TBET appeared to confer a superior prognosis regarding disease-specific survival (DSS; Figure 1). The malignant cells in the majority of cases (>80%) expressed TBET, of which 25% had strong TBET expression. Using a cut-off of 1,500 cells/mm<sup>2</sup>, patients with a higher infiltrate of TBET-positive cells had superior DSS (5-year DSS, 97% vs 77%;  $P=.045$ ). Though most malignant cases expressed TBET, the level of TBET expression did not impact outcome regarding overall survival (OS) or freedom from treatment failure (FFTF). Samples from patients

with TBET-positive cells above or below the 1,500 cell/mm<sup>2</sup> cutoff did not have a significant difference in OS (92% vs 76%, respectively;  $P=.13$ ). The expression of TBET in the microenvironment was higher in EBV-positive cases (35%; median expression, 1,448 cells/mm<sup>2</sup>) than in EBV-negative cases (median expression, 669 cells/mm<sup>2</sup>;  $P=.0033$ ).

The findings, which were based on transcription factors, needed functional validation that these were TH1 and not TH2 polarized cells. Single-cell suspensions were derived from patients at diagnosis from 5 diagnostic CHL biopsies: 2 tonsils and 3 reactive nodes. These single-cell suspensions were compared to other malignant and benign samples through intercellular cytokine stains. The T cells from a host of lymphoma lymph nodes

overexpressed the TH1 cytokines interferon-gamma (median, 31%; range, 18–66%) and tumor necrosis factor (TNF)-alpha (median, 26%; range, 8–20%). No evidence of TH2 cytokines were found, including IL4, IL13, IL21, and the regulatory cytokine IL10. Benign samples had lower expression of TH1 cytokines, with interferon-gamma expressed by 19.7% ( $P$ =nonsignificant) and TNF-alpha by 4.6% ( $P=.03$ ).

Greaves concluded that the dominant T cells in the microenvironment express TBET or FOXP3 rather than TH2-defining cytokines. No evidence suggests significant infiltration of TH2 cells. TBET may hold prognostic significance, and its possible prognostic significance is now being validated in a separate international cohort. TBET seems to have an association with EBV

status. These findings challenge the currently accepted model in which the microenvironment of CHL is suppressive because of a TH2 bias.

## References

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3. Greaves P, Clear A, Owen A, et al. The microenvironment in classical Hodgkin lymphoma shows evidence of a TH1 and TH2 response with TBET expression being associated with improved survival and EBV status. Paper presented at: 17th Congress of the European Hematology Association; June 14-17, 2012; Amsterdam, the Netherlands. Abstract 1107.

# Comparing Intensity of Chemotherapy Followed by PET-Guided Radiotherapy in Patients With Advanced Stage Hodgkin Lymphoma: Final Results of the GHSG HD15 Trial

An ongoing controversy exists in the treatment of advanced-stage Hodgkin lymphoma (HL) as to which regimen should be used: doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) or bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP), with higher-than-standard doses of etoposide, doxorubicin, and cyclophosphamide. Andreas Engert, MD, and coworkers of the German Hodgkin Study Group (GHSG) developed the BEACOPP regimen, which is more toxic than ABVD. They sought

to adjust the regimen by determining which patients would benefit the most, and by identifying the optimal amount of treatment.

The HD9 trial found that escalated-dose BEACOPP (BEACOPP[escalated]) had better tumor control compared to cyclophosphamide, vincristine, procarbazine, and prednisone (COPP) alternated with ABVD over 10 years of follow-up.<sup>1</sup> At 10 years, the FFTF and OS rates were 18% and 11%, respectively.

Based on the HD9 trial, 8 cycles of BEACOPP(escalated) were standard; however, BEACOPP is somewhat more toxic than ABVD, particu-

larly in terms of fertility. The other unresolved question in advanced-stage HL is how many patients need radiotherapy. The GHSG HD15 trial sought to reduce the toxicity of both chemotherapy and radiotherapy while maintaining efficacy.<sup>2</sup>

The trial had 3 randomized arms (Figure 2). Patients received either 8 cycles of BEACOPP(escalated) (8xB(esc)), 6 cycles of BEACOPP(escalated) (6xB(esc)), or 8 cycles of BEACOPP(14) (8xB(14)). The primary endpoint was non-inferiority in FFTF for 6xB(esc) or 8xB(14) compared with 8xB(esc). The secondary endpoints were progression-



### ABSTRACT SUMMARY Persistence of CD30 Expression in CD30-Positive Lymphomas Following Relapse After Brentuximab Vedotin (ADCETRIS)

Both HL and systemic anaplastic large cell lymphoma (sALCL) express CD30 on their cell surface. CD30 is targeted by brentuximab vedotin. This retrospective analysis found that relapsed or progressive HL and sALCL expressed CD30 even after prior exposure to brentuximab vedotin (Abstract 0203).

The impact of brentuximab vedotin on CD30 expression was examined through tumor biopsies of 8 patients treated with brentuximab vedotin who subsequently had disease progression. Disease control was achieved by 6 patients with HL and 2 patients with sALCL. These patients had a median age of 32 years (range, 24–43 years) and a median of 6.5 cycles (range, 2–10) of brentuximab vedotin. Each brentuximab vedotin cycle was 3 weeks long. The best responses were CR for 3 patients, PR for 4 patients, and SD for 1 patient. However, progressive disease occurred in 4 of the patients who had PR or SD while on brentuximab vedotin treatment. An additional 4 patients who had achieved CR or PR discontinued brentuximab vedotin because of peripheral neuropathy (n=1), going on to ASCT (n=2), or changing salvage therapy to ICE while in PR (n=1). These 4 patients later developed progressive disease.

Biopsies of the lymphomas of all patients at the time of progression found that all 8 had ongoing CD30 expression. Thus, even after prior exposure to brentuximab vedotin, relapsed or progressive HL and sALCL express CD30.

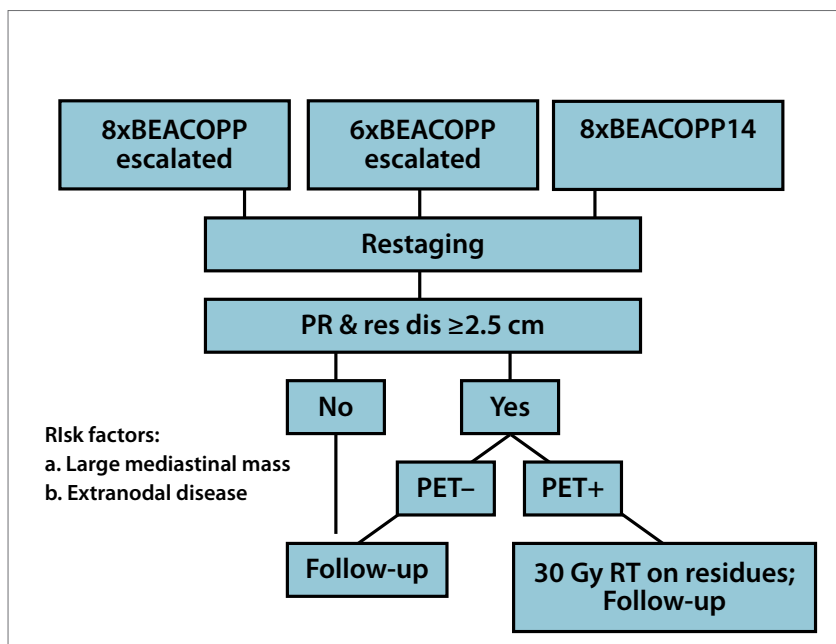
free survival (PFS), OS, toxicity, and negative predictive value (NPV) of PET.

A total of 2,182 patients were enrolled by 408 centers from 5 European countries between 2003 and 2008; 2,043 of these patients were evaluable for outcome. Only patients aged 60 years or younger (range, 18–60) were qualified, and more patients were male. The 3 arms were balanced with regard to International Prognostic Score (IPS) and histology. All patients had advanced stage disease, which was defined as Ann Arbor stage 2B with large mediastinal mass or extranodal lesions, or patients in stages III and IV. Following randomization into the 3 treatment arms, patients were then restaged.

After chemotherapy, only those patients who responded and had residual disease of more than 2.5 cm were analyzed by positron emission tomography (PET). All PET and computed tomography (CT) scans were centrally reviewed. Patients whose PET scans were positive received 30 Gy radiation therapy on the residuals and follow-up, while those who were negative received only follow-up. A total of 808 patients were assessed, and 728 patients qualified for PET analysis.

Major toxicities were hematological. At least 1 grade 3 or 4 leukopenia episode occurred in 90% of patients receiving 8xB(esc), 89% receiving 6xB(esc), and in 73% of patients receiving 8xB(14). Other toxicities of grade 3 or 4 included anemia (62% vs 53% vs 56%, respectively), thrombopenia (63% vs 53% vs 56%, respectively), infection (25% vs 22% vs 21%, respectively), and neuropathy (8% vs 5% vs 13%, respectively). Importantly, leukopenia did not translate into uncontrolled infection. No striking differences occurred between patients receiving 6 versus 8 cycles of BEACOPPesc.

Mortality from HL occurred in 1.8% of patients receiving 8xB(esc), 1.5% of patients receiving 6xB(esc), and in 2.1% of patients receiving



**Figure 2.** GHSC HD15 trial for advanced-stage Hodgkin lymphoma. PET=positron emission tomography; PR=partial response; res dis=residual disease; RT=radiation therapy.

Data from Engert A et al. Paper presented at: 17th Congress of the European Hematology Association; Abstract 1108.

### ABSTRACT SUMMARY 90Yttrium Zevalin Followed by BEAM (Z-BEAM) and Autologous Stem Cell Transplantation (ASCT) For the Treatment of High Risk Relapsed/Resistant Aggressive non-Hodgkin's Lymphoma (NHL)

Among patients with relapsed or refractory NHL who are at high risk of further relapse, treatment with Z-BEAM (90yttrium ibritumomab tiuxetan (Z) combined with BEAM [carmustine, etoposide, cytosine-arabinoside, and melphalan]) achieved a good response with engraftment and had toxicity similar to standard BEAM. Since high-dose chemotherapy and ASCT are considered effective treatments for relapsed aggressive NHL, Z-BEAM is a promising conditioning regimen instead of conventional BEAM.

This single-institution, phase II study sought to determine feasibility and explore possible synergistic effects from adding standard dose 90yttrium ibritumomab tiuxetan to BEAM (Abstract 0240). A total of 30 patients with high-risk, advanced stage NHL, with different histologies, who relapsed or failed to respond after first-line chemotherapy were treated with 90yttrium ibritumomab tiuxetan on day 14, then standard-dose BEAM and ASCT.

After a median follow-up of 27 months from salvage therapy, the 2-year PFS was 63% and the OS was 67%. A total of 11 patients relapsed or progressed after Z-BEAM and 10 patients died (8 patients died of lymphoma, 1 of lung Aspergillosis and H1N1 infection during BEAM, and 1 of late encephalitis).

When the patients treated with Z-BEAM were retrospectively compared with a matched-pair group of 21 patients treated with BEAM alone, no differences in clinical presentation at relapse were found, apart from the number of previous therapies ( $\geq 2$  in only 2 patients [9%] in the BEAM group vs 16 patients [53%] in the Z-BEAM group). A trend for PFS favored Z-BEAM versus BEAM (63% vs 52%), and an updated analysis based on longer follow-up is ongoing.

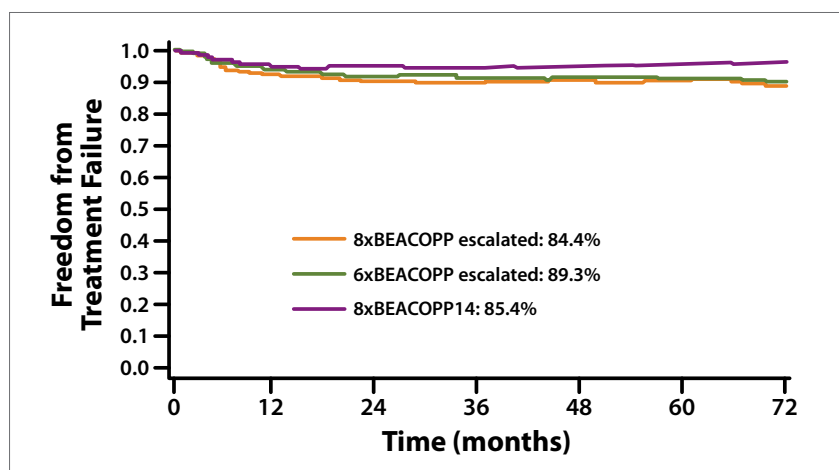
ing 8xB(14). Patients treated with 8xB(esc) had higher toxicity from treatment (2.1%) compared with patients receiving 6xB(esc) (0.8%), as expected from a 25% reduction in the overall amount of chemotherapy. The overall mortality was 7.5% (53 deaths) in the arm receiving 8xB(esc), 4.6% (33 deaths) in the arm receiving 6xB(esc), and 5.2% (37 deaths) in the arm receiving 8xB(14).

Secondary leukemias have been associated with BEACOPP(escalated). A total of 2.7% (n=19) of patients in the 8xB(esc) arm developed acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS), while only 0.3% (n=2) of those in the 6xB(esc) arm developed AML/MDS. In the 8xB(14) arm, 1.1% (n=8) of patients developed AML/MDS. Of the 72 overall secondary neoplasias that occurred, they developed in 4.7% of patients in the 8xB(esc) arm, 2.4% in the 6xB(esc) arm, and in 3.1% of patients in the 8xB(14) arm.

A major result of this trial was the FFTF finding, where 6 cycles were demonstrated to be better than 8 (Figure 3). This surprising result was due to a number of factors associated with receiving 6 cycles instead of 8. These factors include better tumor control, better treatment tolerance, lower mortality, and less secondary neoplasias. The results for FFTF at 5 years were 84.4% with 8xB(esc), 89.3% with 6xB(esc), and 85.4% with 8xB(14). The difference at 5 years was 4.9% for 8xB(esc) versus 6xB(esc) ( $P=.009$ ), 1.1% for 8xB(esc) versus 8xB(14) ( $P=.5$ ), and 3.9% for 8xB(14) versus 6xB(esc) ( $P=.04$ ; nonsignificant).

The OS rates at 5 years were 91.9% for 8xB(esc), 95.3% for 6xB(esc), and 94.5% for 8xB(14). The 5-year difference between 8xB(esc) and 6xB(esc) was 3.3% (97.5% confidence interval [CI], 0.2–6.5%;  $P=.02$ ).

Patients with partial response, residual disease of at least 2.5 cm, and positive disease by PET analysis received additional radiotherapy. This



**Figure 3.** Freedom from treatment failure in the HD15 trial in advanced Hodgkin lymphoma.

Data from Engert A et al. Paper presented at: 17th Congress of the European Hematology Association; Abstract 1108.

is in contrast to prior studies, where all patients with residual disease received radiotherapy. The PET analyses were centrally reviewed in order to maintain the same criteria throughout the study. Among the patients who qualified in this study, 74% were PET-negative (n=548) and 26% were PET-positive (n=191) after chemotherapy. Between patients in complete remission (CR) and those in PET-negative partial remission (PR) after chemotherapy, 4-year PFS rates were similar, at 92.6% and 92.1%, respectively.

At 12 months, the NPV of PET status was 94%, indicating that patients who were PET-positive had a good chance to stay in remission. This study found that PET was a better predictor and more accurate measurement of a patient's status than the conventional CT scan. Dr. Engert explained that this result underscores the meaningful and important criteria

established by his research team. He also stated that the NPV of PET status of 94% indicates that only those advanced-stage patients with residual disease who are PET-positive might need additional radiotherapy. Additional radiotherapy was received by only 11% of all patients in HD15, which was much lower than the 71% rate in the prior HD9 study.

Dr. Engert summarized that this study indicates that the chemotherapy for HL can be improved. The FFTF was higher for the 6xB(esc) arm (89%) than it was for the 8xB(esc) arm (84%) or the 8xB(14) arm (85%). The OS was 92% for patients treated with 8xB(esc), 95% for 6xB(esc), and 94.5% for patients treated with 8xB(14), again favoring 6xB(esc), with a significant difference between 6 and 8 cycles. The treatment-related mortality was higher with 8 cycles (2.1% for 8xB(esc) vs 0.8%

for 6xB(esc) vs 0.8% for 8xB(14)). Regarding the toxicity of BEACOPP, it was emphasized that the mortality with 6 cycles was only 0.8%, and the rates of second neoplasms were low, at 1.8% for 8xB(esc), 0.7% for 6xB(esc), and 1.1% for 8xB(14). Performing PET after chemotherapy can guide the need for additional radiotherapy in this setting, and it also reduces the number of patients requiring radiotherapy. The new GHSG standard is 6xB(esc) for advanced stage HL.

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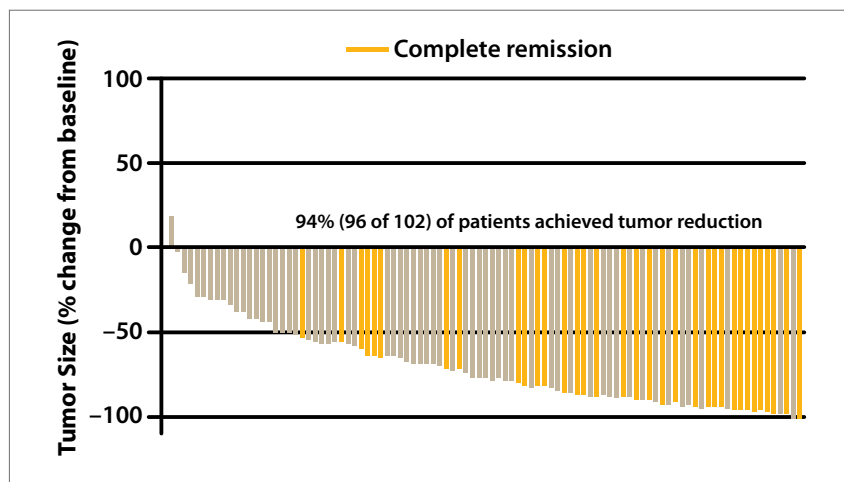
## Long-Term Follow-Up Results of an Ongoing Pivotal Study of Brentuximab Vedotin in Patients With Relapsed or Refractory Hodgkin Lymphoma (HL)

Scott E. Smith, MD, PhD, presented the long-term follow-up results of an ongoing study of patients with relapsed or refractory HL.<sup>1</sup> Survival is lower for patients with relapsed HL than it is for patients with other forms of HL, and the survival curves look dramatically different. Relapse does occur in approximately 50% of patients, resulting in poor to moderate OS. After autologous stem cell transplant (ASCT), the median survival is 2.4 years among patients who relapse less than 1 year after ASCT.<sup>2</sup> These patients live an average of 1.2 years.

Brentuximab vedotin is an antibody-drug conjugate (ADC) with

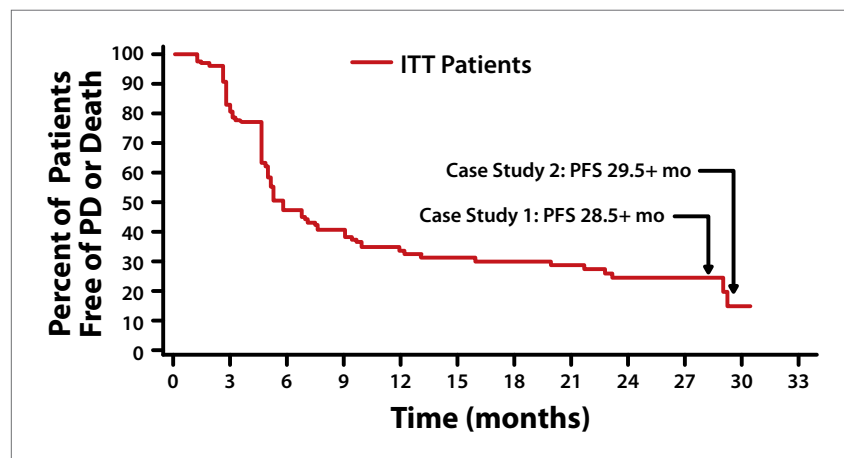
an interesting mechanism of action. Though it appears to be a typical antibody bound to a poison, it is actually an anti-CD30 monoclonal antibody combined with a protease-cleavable linker and monomethyl auristatin E (MMAE), a microtubule-disrupting agent. Its protease-cleavable linker separates it from other standard ADCs. The CD30 on the surface of the Hodgkin cell is bound by the ADC. The ADC-CD30 complex is internalized and traffics to the lysosome, where MMAE is released, which disrupts the microtubule network of the cell. This disruption leads to G2/M cell cycle arrest and apoptosis.

The pivotal study evaluated 102 patients with relapsed/refractory HL after an ASCT failure, and found an objective response rate (ORR) of 75% with brentuximab vedotin.<sup>3</sup> In fact, nearly every patient who received the drug had some type of response and benefit in tumor reduction (94%), though not all responses met the characteristics of PR or CR (Figure 4). The adverse events occurring in at least 20% of patients included peripheral sensory neuropathy, fatigue, nausea, upper respiratory tract infection, diarrhea, fever, neutropenia, vomiting, and cough. However, grade 3 and 4 toxicities were



**Figure 4.** Brentuximab vedotin in relapsed/refractory Hodgkin lymphoma.

Data from Smith S et al. Paper presented at: 17th Congress of the European Hematology Association; Abstract 1109.



**Figure 5.** Case studies: progression-free survival (PFS).

ITT=intent to treat; mo=months; PD=progressive disease.

Data from Smith S et al. Paper presented at: 17th Congress of the European Hematology Association; Abstract 1109.

relatively limited. Other grade 3 or 4 events occurring in at least 5% of the patients included thrombocytopenia (8%) and anemia (6%).

The primary objective of this long-term follow-up was to determine the antitumor efficacy of single-agent brentuximab vedotin. The primary endpoint was overall ORR, as determined by the independent review facility. Secondary endpoints included CR rate, duration of response, PFS, OS, and safety and tolerability.

Patients were deemed eligible if they had relapsed or refractory CD30+ HL, were at least 12 years old, had measurable disease of at least 1.5 cm evaluable by CT, had Eastern Cooperative Oncology Group (ECOG) status of 0 or 1, and had failed prior ASCT. The treatment was brentuximab vedotin 1.8 mg/kg every 21 days administered over 30 minutes for a maximum of 16 cycles for stable disease (SD) or better.

The patients were restaged at cycles 2, 4, 7, 10, 13, and 16 using the

Revised Response Criteria for Malignant Lymphoma.<sup>4</sup> Notably, the brentuximab vedotin dose was capped at a total of 100 kg, so if a patient weighed over 100 kg, he or she received a maximum dose of 180 mg.

For follow-up, survival or disease status were evaluated every 3 months for 2 years, then every 6 months for 3–5 years, and then annually after 5 years. CT scans were performed on this schedule for patients who discontinued treatment for reasons other than progressive disease or initiation of new therapy.

Among the 102 enrolled patients, the average age was 31 years (range, 15–77 years), 48% were female, and 42% had an ECOG status of 0. A total of 71% of patients were refractory to frontline therapy and 42% were refractory to their most recent prior therapy. Patients had received an average of 3.5 prior chemotherapy regimens (range, 1–13), and 71% had relapsed within 1 year after ASCT. The median time from ASCT to first post-transplant relapse was 6.7 months (range, 0–131 months).

The median observation time from first dose of brentuximab vedotin was 26.5 months (range, 1.8–30.9 months), and the estimated 24-month survival rate was 65% (95% CI, 55–74%). The estimated 24-month PFS rate was 25% (95% CI, 16–34%). The median PFS was 5.6 months for all patients, 29.0 months for those with a CR (n=34), 5.1 months for those with a PR, and 3.5 months for patients with SD. A total of 33% (n=34) of these heavily pretreated patients obtained a durable CR with brentuximab vedotin treatment. Of the 15 patients who remain in long-term follow-up with no evidence of disease, 12 patients achieved and remain in CR, and the remaining 3 patients had a PR. Patients with a CR had not started a new cancer therapy since discontinuing the study treatment, except for 3 who received prophylactic ASCT after brentuximab vedotin while in CR.



Patients were allowed to go on to allogeneic stem cell transplant (allo-SCT), and 8 patients did. The outcome was not dramatically different for those who went on to allo-SCT, as their median PFS was 5.6 months.

In a case study of a 27-year-old woman with refractory HL, the patient was initially treated with ABVD and developed progressive disease approximately 1 year after treatment. She then underwent radiotherapy. After progression, she received etoposide, methylprednisolone, high-dose cytarabine, and cisplatin (ESHAP) and had SD until her disease progressed 1 year later. At that point, she underwent allo-SCT, but developed progressive disease 8 months later. She received an experimental treatment with ABT-510, but eventually had disease progression. Gemcitabine was administered, and a partial response was achieved. The patient also received vinblastine, followed by vorinostat for SD. Her disease eventually progressed in March 2009, and she then received brentuximab vedotin from May 2009–April 2010. A total of 16 cycles were administered, and her disease was in CR after cycle 4. She has had no notable adverse events and no dose reductions. She is receiving ongoing treatment in the extension study, and has received a total of 29 doses.

Dr. Smith also presented a second, similar case study of a 26-year-old man who received similar prior upfront therapies, including ABVD and ifosfamide, carboplatin, and etoposide (ICE), followed by radiation therapy. His disease progressed 2 months after tandem ASCT. He received an experimental combination of therapies for progressive disease of AMG655 and vorinostat. The patient then went on the brentuximab vedotin trial and achieved a CR after cycle 4. He did have grade 1 periph-

eral sensory neuropathy and grade 3 hepatic steatosis. The patient did not have dose reductions, is still in CR, and is back to work full-time. Dr. Smith stated that these are interesting results for patients who were quite sick (Figure 5).

In summary, for brentuximab vedotin monotherapy in patients with relapsed refractory HL after ASCT failure with over 2 years of follow-up analysis, the estimated survival endpoints at 24 months are 25% for PFS and 65% for OS. These are encouraging results in patients with a historically poor prognosis. Additional studies in HL are ongoing or planned. A phase III study, known as AETHERA, will compare brentuximab vedotin to placebo in high-risk HL patients post-ASCT. Another phase III study will examine

### ABSTRACT SUMMARY Retreatment With Brentuximab Vedotin in CD30-Positive Hematologic Malignancies: A Phase II Study

This phase II study investigated retreatment with brentuximab vedotin in patients who had previously responded to it, and found that retreatment was generally well tolerated (Abstract 0213). A total of 70% of patients had objective responses.

The study enrolled 16 patients with HL and 8 patients with sALCL who had achieved an objective response with prior brentuximab vedotin treatment and relapsed after discontinuing treatment. The enrolled patients had a median age of 34 years (range, 16–72 years) and a median of 4 prior chemotherapy regimens (range, 2–12). Patients received brentuximab vedotin 1.8 mg/kg every 21 days, with a median of 6.9 months (range, 1–44 months) since the previous brentuximab vedotin treatment and a median of 7 retreatment cycles (range, 1–32+).

Over 25% of patients experienced AEs, including nausea (41%), fatigue (36%), peripheral sensory neuropathy (36%), and diarrhea (27%). The most common grade 3 or 4 AEs, each experienced by 3 patients, were anemia, fatigue, and hyperglycemia. Among the 13 patients with pre-existing peripheral neuropathy, it worsened with retreatment for 4 patients (31%).

Among patients with HL, the best clinical responses were CR (n=3), PR (n=6), SD (n=2), and PD (n=4). Among patients with sALCL, 6 achieved CR, 1 had PR, and 1 patient had PD. Objective responses were achieved by 70% (16/23) of patients, and the median duration of responses was 8.8 months.

brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine (AVD) versus ABVD alone in patients with advanced-stage, frontline HL.

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# Outcome of Patients With Early Stage Hodgkin Lymphoma According to GHSG and NCIC-CTG Risk Classification: The Princess Margaret Hospital Experience

Early stage HL has an excellent prognosis, with consistent reports of OS greater than 90% in large trials of combined modality therapy. With these outcomes, a major focus of modern therapeutic approaches is to minimize the morbidity and mortality associated with treatment. That was the goal of the GHSG HD10 trial, which recently established a new standard of care.<sup>1</sup> Patients with favorable disease demonstrated non-inferior

outcomes with respect to disease control and decreased toxicities with the delivery of less dose-intensive regimens. However, the ability to minimize the toxicity related to treatment while simultaneously maintaining excellent outcomes and disease control is contingent upon accurately identifying those patients who are at risk for treatment failure.

The need to identify patients at risk for treatment failure begs the question of how to best stratify patients with

early HL by risk. Everyone's opinion and answer to this question depends, to some extent, on the area of the world in which they practice. Dr. L. Davison explained that, at Princess Margaret Hospital (PMH) and throughout much of Canada, the traditional approach to risk stratification in early HL has used the scheme based on the HD6 trial by the National Cancer Institute of Canada (NCIC) and ECOG.<sup>2</sup> The risk groups are early favorable, early unfavorable,

## ABSTRACT SUMMARY Inotuzumab Ozogamicin in Patients With Indolent B-Cell Non-Hodgkin Lymphoma Refractory to Rituximab and Chemotherapy or Radioimmunotherapy

Inotuzumab ozogamicin had notable clinical activity with durable responses, particularly in follicular lymphoma patients, in this phase II study of patients with indolent B-cell NHL refractory to rituximab plus chemotherapy or radioimmunotherapy (Abstract 0793). Inotuzumab ozogamicin consists of a humanized anti-CD22 antibody that is conjugated with calicheamicin. Calicheamicin is a potent cytotoxic antitumor antibiotic.

A total of 81 patients with follicular lymphoma (n=72), marginal zone lymphoma (n=4), or small lymphocytic lymphoma (n=5) received inotuzumab ozogamicin 1.8 mg/m<sup>2</sup> every 28 days for 4–8 cycles, with the dose and frequency adjusted based on toxicities. The patients had to have had at least 2 prior systemic therapies and had no response or progression within 6 months of completing therapy containing rituximab or within 12 months of completing radioimmunotherapy. The heavily pretreated patients had a median of 3 prior anticancer regimens (range, 1–14; 35% had ≥4), 5 (6%) had a prior autologous SCT, and 29 (37%) were refractory to their most recent prior chemotherapy. The median age of the patients was 63 years (range, 29–84 years). According to the Follicular Lymphoma International Prognostic Index (FLIPI) scores, 24% of the follicular lymphoma patients were low risk, 28% were intermediate risk, and 49% were high risk.

The median follow-up time was 10.1 months. The median number of inotuzumab ozogamicin doses received was 3 (range, 1–8), and AEs led to dose reductions in 17% of patients and delays in 15%. The most common grade 3 or 4 AEs were thrombocytopenia (57%), neutropenia (32%), nausea (5%), elevated gamma-glutamyl transferase (5%), elevated aspartate aminotransferase (4%), and pneumonia (4%). A total of 41% of patients discontinued treatment because of AEs, which included 28% who withdrew due to persistent thrombocytopenia that did not recover to grade 1 or 0 within the 28-day dose delay allowed by the protocol. For the 75 evaluable patients, the ORR was 61%, while ORR among patients with follicular lymphoma was 67%. The complete response rate was 28%, while the rate among patients with follicular lymphoma was 32%. According to FLIPI scores, the follicular lymphoma patients had ORRs of 75% in low-risk patients, 58% in intermediate-risk patients, and 56% in high-risk patients.

The median PFS was 12.0 months. Median PFS was 26.9 months for patients with follicular lymphoma, 8.8 months for marginal zone lymphoma patients, and 2.4 months for small lymphocytic lymphoma patients. Low-risk follicular lymphoma patients had not yet reached median PFS, and their 1-year PFS rate was 76%. Likewise, median OS had not yet been reached for low-risk follicular lymphoma patients, and their 1-year survival rate was 84%.

**Table 1.** Risk Classification Schemes For Early Stage Hodgkin Lymphoma

Risk Group	NCIC-CTG	GSHG
Early favorable	Stage I–IIA and none of: • age >40 years • >4 sites of disease • MCHL or LDHL • ESR >50	Stage I–II and none of: • bulky mediastinal mass • extranodal disease • ESR ≥50 mm/hr (>30 if B symptoms) • >3 nodal sites
Early unfavorable	All other stage I–IIA	All other stage I–II
Advanced	Stage I–II with any of: • B symptoms • abdominal disease • bulky disease	Any stage IIB with either: • bulky mediastinal mass • extranodal disease

ESR=erythrocyte sedimentation rate; LDHL=lymphocyte depleted Hodgkin lymphoma; MCHL=mixed cellularity Hodgkin lymphoma.

Data from Davison L et al. Paper presented at: 17th Congress of the European Hematology Association; Abstract 1110.

**Table 2.** Multivariate Analysis: Risk Group and Individual Risk Factors

Multivariate Analysis: Risk Group			
	Explanatory Variable	Hazard Ratio (95% CI)	P Value
Overall survival	NCIC-CTG	1.8 (-0.42–1.6)	.25
	GSHG	3.6 (-0.28–2.8)	.11
Progression-free survival	NCIC-CTG	1.3 (-0.40–0.96)	.41
	GSHG	1.5 (-0.56–1.3)	.43
Multivariate Analysis: Individual Risk Factors			
Overall survival	Age ≥40 years at diagnosis	2.69 (1.3–5.7)	.01
	Extranodal disease	4.6 (1.7–12.8)	.003
Progression-free survival	Elevated ESR	2.2 (1.1–4.2)	.02
	Extranodal disease	2.7 (1.3–5.7)	.01

CI=confidence interval; ESR=erythrocyte sedimentation rate.

Data from Davison L et al. Paper presented at: 17th Congress of the European Hematology Association; Abstract 1110.

and advanced. Advanced risk includes patients with stage I and II disease, with any of the following: B symptoms, abdominal disease, or bulky disease. Any patient with abdominal disease symptoms that are isolated to iliac or inguinal regions or with bulk are also considered advanced risk, which is in distinct contrast to the GSHG risk stratification scheme. In the GSHG scheme, stage IIB patients are defined as advanced risk only if they have bulky mediastinal mass or extranodal disease (Table 1).

The NCIC scheme considers patients to have early favorable risk if

their disease is stage I or IIa, and if they do not have any of the following other risk factors: age 40 years or older, 4 or more sites of disease, mixed cellularity HL or lymphocyte depleted HL, or an erythrocyte sedimentation rate (ESR) of 50 or higher. All other stage I and IIa disease is considered early unfavorable risk. Notably, the risk factors are largely non-overlapping between the NCIC scheme and the GSHG scheme. For example, NCIC considers age greater than 40 years or certain histological subtypes to be poor risk factors, but GSHG does not. On the other hand, extranodal

disease is considered a poor risk factor by the GSHG scheme, but not by NCIC.

Even features that both groups recognize as having prognostic significance are defined differently between NCIC and GSHG. For example, NCIC considers 4 or more sites of disease to be a poor risk feature, while GSHG uses 3 as the cutoff number. An additional layer of complexity arises because these 2 groups count and enumerate nodal sites of disease differently (Table 2).

The overall message is that 2 different cooperative oncology groups define risk categories in very different ways. In fact, the risk categories reflect very different subgroups of HL patients. Additionally, the significance of these risk factors was developed at a time when radiotherapy alone was considered standard of care for the treatment of early HL. It remains to be determined whether these risk factors and risk stratification schemes have retained their prognostic significance in the era of modern doxorubicin-based combined modality therapy.

Historical evidence suggests that these risk stratification schemes may not have kept their significance. In the HD6 trial by the NCIC,<sup>2</sup> the long-term outcomes of the unfavorable group defined by the NCIC criteria were not inferior to their favored counterparts, based on 11.3 years of follow-up. The unfavorable group had an OS of 92% and PFS/FFTF of 86%, while the favorable group had an OS of 98% and PFS/FFTF of 89%. Similarly, in the HD10 and HD14 trials of the GSHG patients who received 4 cycles of ABVD plus 30 Gy involved-field radiotherapy, the unfavorable and favorable groups of patients had outcomes that were not significantly different. The favored patients in HD10 had an OS of 94% and PFS/FFTF of 87%, while the patients with unfavorable risk in HD14 had an OS of 97% and PFS/FFTF of 87%. Of course, dangers exist in comparing

### **ABSTRACT SUMMARY Activity of Brentuximab Vedotin in Patients With Relapsed or Refractory Hodgkin Lymphoma or Systemic Anaplastic Large-Cell Lymphoma: Comparisons With Meta-Analyses of Historical Chemotherapy Data**

Brentuximab vedotin was found to have anti-tumor activity that appears to exceed that of gemcitabine-based therapies for HL patients who have relapsed or refractory disease after ASCT. The anti-tumor activity of brentuximab vedotin also appears to exceed that of other treatment options for aggressive relapsed or refractory NHL, including sALCL. Meta-analyses were used to compare historical chemotherapy data to 2 single-arm phase II pivotal trials of brentuximab vedotin: 1 for relapsed or refractory HL and 1 for relapsed or refractory sALCL (Abstract 0205). For the relapsed or refractory HL meta-analysis, results from 605 patients were evaluated from 16 trials that included 9 post-ASCT trials (n=296, median of 3 prior regimens) and several ASCT-naïve trials (n=309, median of 1 prior regimen). The post-ASCT subgroup had a CR of 15% (95% CI, 6.5–23.5), which was lower than that seen with brentuximab vedotin (CR=34%; 95% CI, 25.2–44.4;  $P=.003$ ). Patients in the brentuximab vedotin trial had received a median of 3.5 prior regimens, which was more than the ASCT-naïve patients, who had less advanced disease and were less heavily pretreated. The ASCT-naïve subgroup had a CR of 35% (95% CI, 16.9–52.2). Among the trials evaluated, the estimated overall CR rate was 24% (95% CI, 14.2–33.9) in patients with relapsed or refractory HL, and a nonsignificant trend toward lower activity in the historical trials than in the brentuximab vedotin trial was identified ( $P=.148$ ).

For the relapsed or refractory sALCL meta-analysis, results from 48 sALCL patients in 19 trials were evaluated. The estimated overall CR rate of 18% (95% CI, 11.3–24.5) was lower than with brentuximab vedotin (CR rate at time of meta-analysis=53%; 95% CI, 39.9–66.7;  $P<.0001$ ).

across trials. However, these results suggest the need to challenge the current and conventional risk stratification schemes.

Considering these concerns regarding current risk stratification schemes as well as the interest of the group at PMH in transitioning their treatment approach for early stage HL patients who have favorable risk profiles, Dr. Davison and colleagues were interested in whether the GHSG risk stratification scheme could separate early HL patients at lower versus higher risk.<sup>3</sup> They also questioned whether the GHSG criteria, compared with the NCIC criteria, better predicted outcome in early stage HL.

A retrospective chart review of all early stage HL patients treated at

PMH over a 12-year period between 1997 and 2009 was conducted. The patients were risk stratified according to the 2 criteria based on their baseline characteristics at the time of diagnosis, and OS and PFS were measured by risk.

A total of 495 patients treated for stage I or II HL were identified, with a median age of 32 years; 35% of patients were 40 years of age or older. Patients were largely at stage II, with few nodal sites of involvement, an absence of other symptoms, few areas of extranodal disease (present in 11% of patients), and few with other bulky disease (5%). The majority (80%) of these patients received combined modality therapy, while the remaining 20% were roughly divided between

those who received radiation alone and those who received chemotherapy alone. For the patients who did receive chemotherapy, the regimen was almost invariably ABVD, and none of the patients received BEACOPP, whether the escalated or standard dose.

When patients were stratified by risk group, the NCIC criteria allocated the largest group of patients (39%) to the advanced risk group, 19% to the favorable risk group, and 32% to the unfavorable risk group. That is in stark contrast to the GHSG criteria, where the bulk of patients (45%) were in the unfavorable risk group, while 21% were in the favorable risk group and 10% were in the advanced risk group.

The median follow-up was 37.3 months (range, 0.4–158.6 months). The whole cohort had an OS rate of 94.4% and PFS rate of 88.1%. When the NCIC risk groups were compared for OS and PFS, only the comparison of OS for advanced versus favorable patients approached statistical significance ( $P=.074$ ). In other words, no statistically significant difference was found between early unfavorable and favorable patients by NCIC criteria with respect to either OS or PFS. Among patients risk-stratified by the GHSG criteria, the results were very similar. The favorable and unfavorable patients had no statistically significant difference regarding either OS or PFS by GHSG criteria.

In recognizing that higher risk disease can be overcome by administering more intensive therapy, a multivariate analysis addressed the question of whether the results could be explained by the fact that patients who were perceived as higher risk received more intensive treatment. When the multivariate analysis controlled for the intensity of treatments received, the allocation of unfavorable risk groups by either NCIC or GHSG criteria did not predict for OS or PFS. Thus, the manner in which patients were treated did not explain the lack of a difference

in outcomes between favorable and unfavorable groups.

A further multivariate analysis of individual risk factors found that OS was predicted only by age of 40 years or greater ( $P=.01$ ), which is not among the risk factors defined by the GHSG criteria, and by the presence of extranodal disease ( $P=.003$ ), which is not among the risk factors defined by the NCIC criteria. An analysis of PFS found that only elevated ESR ( $P=.02$ ) and extranodal disease ( $P=.01$ ) were predictive of progressive disease.

In conclusion, the data suggest that in this age of combined modality therapy, current risk classification schemes may no longer discriminate between patients at higher versus lower risk of treatment failure. Furthermore, not all of the commonly accepted risk factors have prognostic significance in this study cohort. These findings are in line with the recent publication of the GHSG HD14 trial of early unfavorable patients,<sup>4</sup> where a multivariate analysis demonstrated that some, but not all, of the risk factors were predictive for PFS.

Finally, this study identified some risk factors that were prognostic for OS and for PFS that are not universally considered risk factors. These data suggest that further studies are required in order to define more biologically meaningful prognostic factors for early stage HL. This is particularly important, as physicians increasingly rely on risk stratification to deliver risk-adapted therapy.

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## ABSTRACT SUMMARY Health State Utilities For Relapsed/Refractory (Rel/Ref) Hodgkin Lymphoma (HL) and Systemic Anaplastic Large-Cell Lymphoma (sALCL)

Treatment response in relapsed or refractory HL and sALCL has perceived benefit in societal evaluations of treatment cost-effectiveness. Residual B symptoms are associated with a substantial decline in quality of life (QOL). Increasing pressure on limited healthcare resources has led many countries to review the cost-effectiveness of newly developed therapies, typically through expressing the benefits of a treatment in quality-adjusted life years (QALYs). Both survival and QOL are captured when a treatment is valued in QALYs.

This study sought to capture QOL data for outcomes from therapy for relapsed or refractory HL and sALCL by developing health state descriptions, which included the extent of disease symptoms (B symptoms) and clinical response (complete or partial response, stable or progressed disease; Abstract 0204). Health utility values expressed the data, and the values ranged from 0 for dead to 1 for fully healthy. Descriptions were developed by reviewing published literature, discussing the health states with 5 clinical experts, interviewing 5 patients, then drafting the descriptions, and finally having 6 specialist clinicians review the descriptions. Then, the time trade-off (TTO) task was used by members of the general public ( $n=100$  in the United Kingdom (UK) and  $n=75$  in Australia) to value the health state descriptions. A utility value was elicited by the TTO task that examined an individual's willingness to trade-off years of life to avoid the consequences of living in a presented state.

A notable improvement in QOL was associated with any treatment response, with partial response having higher mean utility values of +0.084 (UK) and +0.109 (Australia) versus SD. A complete response had a notably high utility value, with an increase of +0.196 (UK) and +0.224 (Australia) over SD. Residual B symptoms after treatment lowered QOL compared with SD without B symptoms, with a difference of -0.124 (UK) and -0.110 (Australia). The UK and Australian valuations of health state utility values were broadly similar and had identical ordering in terms of preference.

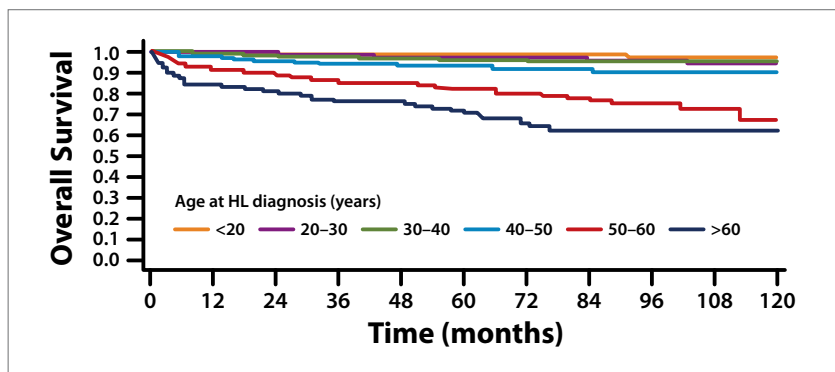


## Treatment-Related Mortality in Patients Undergoing Therapy for Advanced Hodgkin's Lymphoma: Analysis of the German Hodgkin Study Group (GHSG)

**B**eate Klimm, MD, presented the GHSG data on treatment-related mortality in patients undergoing therapy for advanced HL. BEACOPP(escalated) is a very efficient treatment scheme.<sup>1</sup> The 10-year update from the HD9 trial,<sup>2</sup> where BEACOPP(escalated) was first implemented, had a FFTF of 82% and OS of 86%. However, great concerns exist about acute toxicities, such as hematologic, infection, and transplant-related mortality, along with long-term toxicities, including secondary neoplasia, cardiac and pulmonary toxicity, and infertility. This current analysis aimed to find risk factors for treatment-related mortality (TRM) and to determine measures to reduce the risk and improve OS for patients.<sup>1</sup>

This study analyzed 5,134 patients from the HD9,<sup>2</sup> HD12,<sup>3</sup> and HD15<sup>4</sup> trials for advanced HL; the 1,569 patients who were not treated with BEACOPP(escalated) and the 129 patients who were not qualified were excluded. The remaining 3,402 patients were studied, which included 64 deaths (1.9% TRM rate). Among the patients, 61% were male; 33.2% were aged 40 years or older; 84% had stage III or IV disease; 67.8% had B symptoms; 94.3% had good performance status (PS; Karnofsky  $\geq$ 80% or ECOG  $<$ 2); and approximately one third of patients had large mediastinal mass, organ involvement, or IPS scores of 3 or higher. Among the patients who died of TRM, the median age was 50 years (range, 17–64 years), while the median age of the whole group of patients analyzed was 33 years (range, 16–65 years).

Most of the TRM was due to neutropenic infections (87.5%), while



**Figure 6.** Overall survival according to age.

Data from Wongso D et al. Paper presented at: 17th Congress of the European Hematology Association; Abstract 1111.

4.7% of patients died of cardiovascular disease, 4.7% died of internal bleeding, and 3.1% of patients died of respiratory neomycin toxicity. Among the lethal infections, 27% were bacterial, with approximately half Gram-positive and half Gram-negative. About 20% of the lethal infections were mycotic infections, and only 1.8% were viral infections. For over half (51.8%) of patients, the cause of the infection was not specified.

An analysis of TRM by age group found that TRM was not below 1% for any age group. A striking rise in TRM occurred in patients older than 40 years of age. TRM was approximately 3% for patients 30–50 years of age, approximately 4% for patients 50–60 years of age, and more than 15% for patients over the age of 60 years. Kaplan-Meier curves of OS illustrate worse survival for patients older than 60 years, and also for patients over 50 years of age, compared with the other patients (Figure 6). The OS curves have a very early drop, which may be

due to TRM or to other reasons, such as failure to maintain dose intensity in elderly patients that might be very early relapses.

A total of 20 patients died during the first cycle of chemotherapy. The rest of the deaths occurred throughout the other cycles.

When TRM was related to performance score, only about 5% of patients had a lower performance score, but the TRM rate was 4-fold higher in these patients compared with other patients. A univariate analysis for TRM found 4 factors that were highly predictive and significant. These are age 40 years or older (estimated odds ratio 6.255; 95% CI, 3.536–11.065;  $P<.0001$ ), age 50 years or older (estimated odds ratio 6.163; 95% CI, 3.739–10.158;  $P<.0001$ ), ECOG PS of 2 or Karnofsky PS below 80 (estimated odds ratio 4.537; 95% CI, 2.420–8.505;  $P<.0001$ ), and IPS of 3 or higher (estimated odds ratio 3.118; 95% CI, 1.775–5.477;  $P<.0001$ ).



Multivariate regression analysis was carried out by backward selection of covariates with *P* values below 0.1, and 3 factors correlated to TRM were found. These 3 factors are age 40 years or older (estimated odds ratio 3.057; 95% CI, 1.442–6.479; *P*=.0035), age 50 years or older (estimated odds ratio 2.526; 95% CI, 1.276–5.000; *P*=.0078), and ECOG PS of 2 or Karnofsky PS below 80 (estimated odds ratio 4.049; 95% CI, 2.055–7.977; *P*<.0001). All other risk factors, including sex, stage of disease, B symptoms, and such well-known risk factors as 3 or more involved lymph node areas, extranodal involvement, large mediastinal tumor, or elevated ESR, were not significantly associated with a higher risk of TRM in the multivariate analysis.

As soon as 2 of the 3 risk factors identified by the multivariate analysis were positive, the TRM rate went up from over 5% to 15%. When all 3 significant risk factors were positive, the TRM rate was 13.3%.

A TRM score was devised that may be helpful to clinicians. One point is assigned to each risk factor that was significant by multivariate analysis. Age below 40 years is scored as 0, 40–49

years as 1, and 50 years or older is 2. An ECOG PS below 2 or Karnofsky PS of 80 or higher is scored as 0, while ECOG PS of 2 or Karnofsky PS below 80 is scored as 1. When the TRM score is 2 or above, the risk of TRM is greater.

In summary, BEACOPP(escalated) is a very efficient, but also toxic, regimen. The rate of TRM in the HD9, HD12, and HD15 trials was 1.9%. The main cause of TRM was infection, and most TRM occurred in the first chemotherapy cycle. Risk factors for TRM include age of 40 years or older and PS.

Dr. Klimm and colleagues suggested possible measures to reduce toxicity with BEACOPP(escalated) in patients at higher risk. A pre-phase treatment can be implemented for all patients over 40 years old, hospitalization can be implemented during the first cycle of BEACOPP(escalated), granulocyte colony-stimulating factor support can be administered on Day 4 instead of Day 8 (as was previously the case), and antibiotics can be used prophylactically during the whole course of chemotherapy. For antibiotic prophylaxis, the recommendation is trimethoprim/sulfamethoxazole 3 times per week and fluoroquinolones

during the time of aplasia. These recommendations were implemented in the current HD18 trial through an amendment at the end of 2009, and the TRM rate is less than 1%, with 14 deaths in 1,416 patients as of June 2012. Analysis of age-related toxicity and mortality is ongoing, with re-evaluation of dosing, hospitalization, and age limits.

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## Commentary

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There were many clinically significant presentations on lymphomas at the 2012 European Hematology Association (EHA) meeting. Several trials provided updated results on brentuximab vedotin, obinutuzumab, and inotuzumab, as well as on the use of radioimmunotherapy in combination with etoposide, arabinoside, cytarabine, and melphalan (BEAM) for autologous stem cell transplantation (ASCT).

### Brentuximab Vedotin

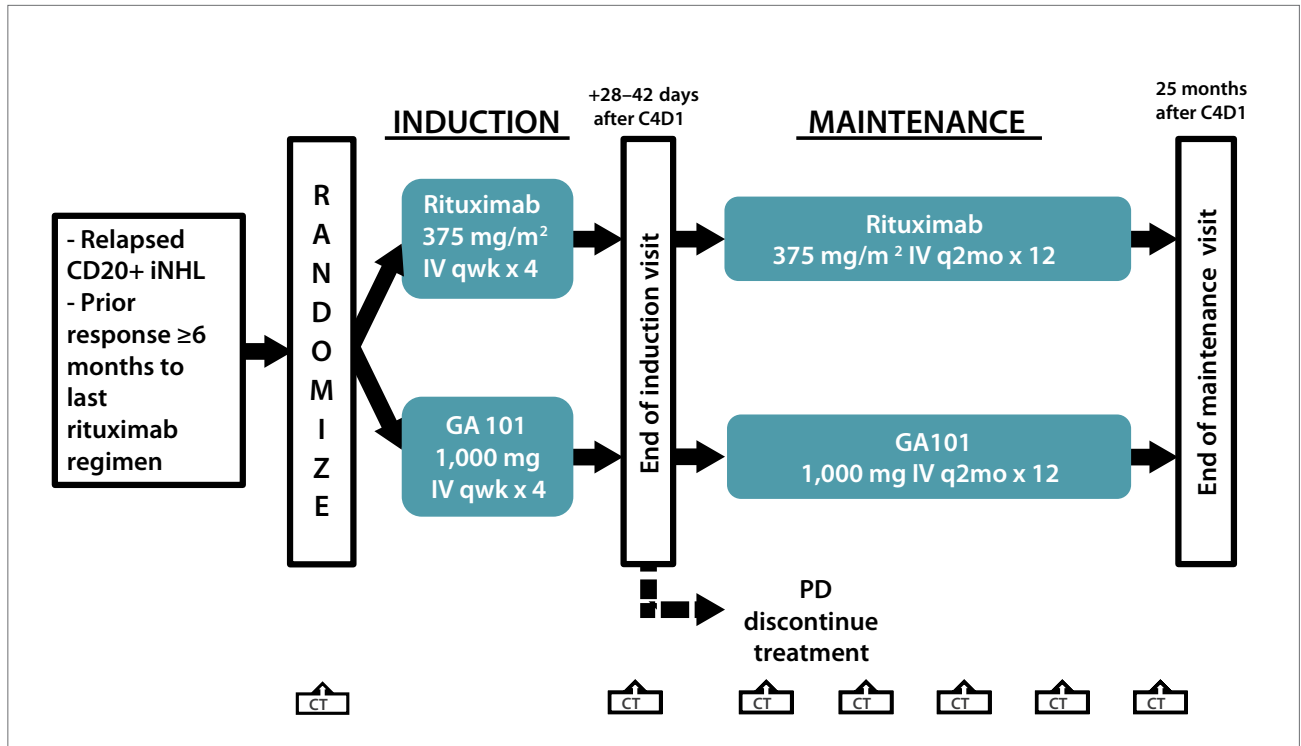
Several studies examined the use of brentuximab vedotin in patients with relapsed/refractory Hodgkin lymphoma (HL) and systematic anaplastic large cell lymphomas (sALCL). Smith<sup>1</sup> presented the updated results with longer follow-up from the pivotal phase II study of brentuximab vedotin in patients with relapsed/refractory HL. In the previous presentation, brentuximab vedotin was shown to have an overall response rate of 75% and a complete response rate (CR) of 34%. At this presentation, the median observation time from first dose was 26.5 months. It was found that more than one third of the patients who obtained a CR remained in CR. The median progression-free survival (PFS) for patients who obtained a CR was 29.0 months, which was notably longer than the median PFS for patients who achieved a partial response (PR) or stable disease (SD). This study showed that, with the use of single-agent brentuximab vedotin, durable remission is achievable in such a heavily pretreated high-risk population.

Forero-Torres<sup>2</sup> presented results from a phase II trial examining the use of brentuximab vedotin in the retreatment setting. This study included 14 patients with HL and 8 patients with sALCL, all of whom had previously

been treated with brentuximab vedotin and achieved an objective response. These patients had all experienced relapse after discontinuing treatment. This study showed that retreatment with brentuximab vedotin was well

### ABSTRACT SUMMARY The Addition of Stem Cell Transplantation Following Induction Chemotherapy Improves Overall Survival in Mantle Cell Lymphoma Patients Who Achieve a Complete Response

This study involved 135 patients with mantle cell lymphoma (MCL) who were treated with anthracycline-containing regimens of HyperCVAD alternating with methotrexate/cytarabine (M/A) and obtained a complete remission (CR; Abstract 0249). Patients were divided into 2 groups. Within each group, patients were evaluated for PFS, OS, and a multivariate analysis for risk of progression, treatment failure, and death. Group 1 included 29 patients with a median age of 70 years (range, 55–86 years) who received an anthracycline-containing regimen alone while 33 patients with a median age of 58 years (range, 39–75 years) received an anthracycline plus stem cell transplant (SCT). The 5-year OS for patients receiving anthracycline alone was 28% (95% CI, 13–46%) compared to 86% (95% CI, 65–94%) for those patients receiving an anthracycline regimen followed by SCT in first CR ( $P < .001$ ). Group 2 patients had a median follow-up of 6 years (range, 2–13 years). Fifteen patients received HyperCVAD-M/A alone (median age, 53 years [range, 32–75 years]), and 58 patients received HyperCVAD-M/A followed by SCT (median age, 56 years [range, 35–70 years]). With a median follow-up of 5 years (range, 1–12 years), the 5-year OS for patients receiving HyperCVAD-M/A alone was 47% (95% CI, 21–69%) compared to 78% (95% CI, 63–87%) for those receiving HyperCVAD-M/A with ASCT ( $P = .03$ ). In a multivariate analysis, both groups had a decreased hazard risk of death with the addition of SCT (anthracycline group,  $P = .02$ ) and (HyperCVAD-M/A,  $P = .001$ ). Age was the only other significant covariate for the risk of death ( $P = .01$ ). The use of high-dose chemotherapy and SCT improved overall survival when used as a consolidation therapy in patients with MCL who achieved a CR with either an anthracycline or HyperCVAD-M/A.



**Figure 7.** Study design for GAUSS (BO21003).

C4D1=cycle 4, day 1; CT=computed tomography; iNHL=indolent non-Hodgkin lymphoma; IV=intravenous; PD=progressive disease.

Data from Goy A et al. Paper presented at: 17th Congress of the European Hematology Association; Abstract 0790.

tolerated, and objective responses were achieved in 65% of patients. Of the 11 patients who had pre-existing neuropathy, 27% experienced worsening with retreatment, suggesting that it is possible to retreat with brentuximab vedotin, even in patients with prior neuropathies. The option for retreatment with brentuximab vedotin is certainly very attractive, especially in patients who had previously achieved an objective response.

Chen<sup>3</sup> presented a study that examined the effect of brentuximab vedotin on CD30 expression. There were 6 patients with HL and 2 patients with sALCL. A total of 4 patients had initially achieved an objective response and discontinued treatment. These 4 patients relapsed subsequently while off treatment, and biopsies of their lymphomas showed persistent CD30 expression. Another 4 patients had developed progressive disease while on treatment. Biopsies of their lymphoma also revealed per-

sistent CD30 expression. This study not only shows that brentuximab vedotin does not negatively impact CD30 expression, it also suggests that loss of CD30 is not a primary mechanism of resistance to brentuximab vedotin. This study also offers a rationale for the findings from the retreatment trial, showing that brentuximab vedotin is still effective in the retreatment setting because of persistent CD30 expression.

Gualberto<sup>4</sup> presented a study that compared the activity of brentuximab vedotin with historical chemotherapy data. They were able to find 16 HL trials where patients were treated with traditional chemotherapy. The meta-analysis showed a CR rate of 15% in the post-ASCT group, which is significantly lower than the CR rate of 34% obtained with brentuximab vedotin in HL. They also found 19 trials with sALCL, and meta-analysis showed a CR rate of 18%, which is again

significantly lower than the CR rate of 53% obtained with brentuximab vedotin in sALCL. This is not a prospective, randomized, control trial; thus, direct comparisons are difficult to make. However, these are the only data available, and the results show that brentuximab vedotin compared favorably with historical chemotherapy regimens.

### Ibritumomab Tiuxetan

Ibritumomab tiuxetan is a radioimmunoconjugate that delivers radiation (Yttrium 90) to lymphomas that expresses CD20. Botto<sup>5</sup> presented a phase II study evaluating the feasibility and synergistic effect of standard dosing to a BEAM high-dose conditioning regimen in patients with high-risk advanced stage non-Hodgkin lymphoma (NHL). As a secondary endpoint, they also performed a matched cohort analysis with a group of patients treated

### **ABSTRACT SUMMARY Health Outcomes in Hodgkin's Lymphoma Survivors: Incidence of Late Complications With a Focus on Cardiovascular Disease and Impact of Screening and Intervention**

More Hodgkin lymphoma (HL) patients die from the late effects of curative combined therapy modalities than from disease progression. It is therefore of critical importance to identify risk factors and methods of risk reduction in order to improve long-term health outcomes in this population. This study sought to determine the incidence and impact of late complications, particularly cardiovascular disease, in patients cured of HL who were treated in a metropolitan health region over a 31-year period (Abstract 0217). The South Australian Cancer Registry and Individual Hospital Cancer Registry were used to identify patients. Patients were eligible to participate if they were older than 18 years of age, diagnosed after 1975, and in complete remission for 5 years. Modified Children's Oncology Group guidelines were used to assess late complications and risk factors. Of the 158 patients with HL who were identified, only 72 patients were evaluable at the cut-off date. The median age was 35 years at diagnosis and 52 years at inclusion. A total of 50 patients were alive at cut-off, and 41 patients reported no late complications or other factors that could modify risk. The most frequently detected risk factors not including treatment were hypercholesterolemia (32 patients), obesity (20 patients), smoking (16 patients), and hypertension (12 patients). Late effects leading to significant morbidity and mortality were common. Second cancers occurred in 24 patients, which led to death in 17 patients. According to screening, 1 patient had relapse of HL, and 1 patient each had early cancer of the breast, thyroid, and bowel. Potentially curative surgical and medical treatment was administered to all patients. Overt cardiovascular and cerebrovascular disease was detected in 15 and 6 patients, respectively, of whom 2 had not been previously diagnosed. Cardiac arrest due to myocardial infarction caused 2 patients to die instantly. Asymptomatic valve disease was present in 4 patients. The risk of cardiovascular disease was increased by the presence of hypertension ( $P=.05$ ). The risk of death from any cause was increased by radiotherapy, smoking, hypertension, and hypercholesterolemia ( $P=.009$ ). Using the Fisher Exact Test, radiotherapy appeared to be the single most important risk factor for cardiovascular disease ( $P=.015$ ).

with standard BEAM without ibritumomab tiuxetan. When patients were treated with ibritumomab tiuxetan plus BEAM, the CR rate was 63%, the PR rate was 23%, and the 2-year PFS and OS was 63% and 67%, respectively. In their secondary endpoint analysis, Z-BEAM had an ORR of 86% compared with 62% in

the BEAM-only group, and a trend in favor of Z-BEAM was observed for PFS (63% vs 52%, respectively). The conclusion was that ibritumomab tiuxetan plus BEAM shows promising activity in relapsed/resistant NHL. This concept of adding radioimmunotherapy to the BEAM conditioning regimen has been extensively studied

with another radioimmunotherapy agent, tositumomab. Unfortunately, a randomized control trial of tositumomab plus BEAM failed to show a benefit in terms of PFS. Perhaps ibritumomab tiuxetan, which uses Yttrium-90 instead of Iodine-131 as a radioisotope, could offer more benefit when combined with BEAM.

### **Obinutuzumab**

Goy<sup>6</sup> presented a randomized phase II trial comparing the safety and efficacy of obinutuzumab with rituximab in indolent NHL (Figure 7). Rituximab is certainly effective for NHL, and this agent has revolutionized the treatment for B-cell lymphoma. However, lymphomas tend to relapse and eventually become resistant to rituximab. New therapeutic strategies targeting CD20 are highly needed. Obinutuzumab is a unique glyco-engineered humanized type II anti-CD20 monoclonal antibody. A total of 175 patients were randomized to receive 4 weekly infusions of either obinutuzumab or rituximab. Patients without progression following induction therapy received maintenance obinutuzumab or rituximab every 2 months for up to 2 years. With a median observation time of 15 months, the ORR in the obinutuzumab arm was 44.6%, compared with 33.3% in the rituximab arm. A blinded independent review facility also confirmed the superior ORR (44.6% vs 26.7%, respectively). This is the first head to head trial of obinutuzumab versus rituximab. It demonstrated high response rates without an appreciable difference in safety. Future studies involving obinutuzumab will be focusing on its ability to be combined with other chemotherapies for use in NHL.

### **Inotuzumab**

Goy<sup>7</sup> also presented a phase II study evaluating the safety and efficacy of inotuzumab in indolent B-cell

NHL. Inotuzumab is a humanized anti-CD22 antibody conjugated with calicheamicin. Calicheamicin is a DNA-damaging agent and leads to apoptosis. This agent has already shown promising results in phase I/II trials in aggressive leukemias/lymphomas expressing CD22. This trial had 81 heavily pretreated patients with indolent NHL. The median follow-up was 10.1 months. Among the 75 evaluable patients, the objective response rate was 61%, and the CR rate was 28%. The median duration of objective response was 24.8 months. The median PFS was 12 months. The most common grade 3/4 adverse events were thrombocytopenia (57%) and neutropenia (32%). This drug shows promising activity in heavily pretreated

patients with indolent NHL, and its toxicities are manageable.

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