

A SPECIAL MEETING REVIEW EDITION

Highlights in Lymphoma From the 2014 European Hematology Association Congress

A Review of Selected Presentations From the 2014 European Hematology Association Congress • June 12-15, 2014 • Milan, Italy

Special Reporting on:

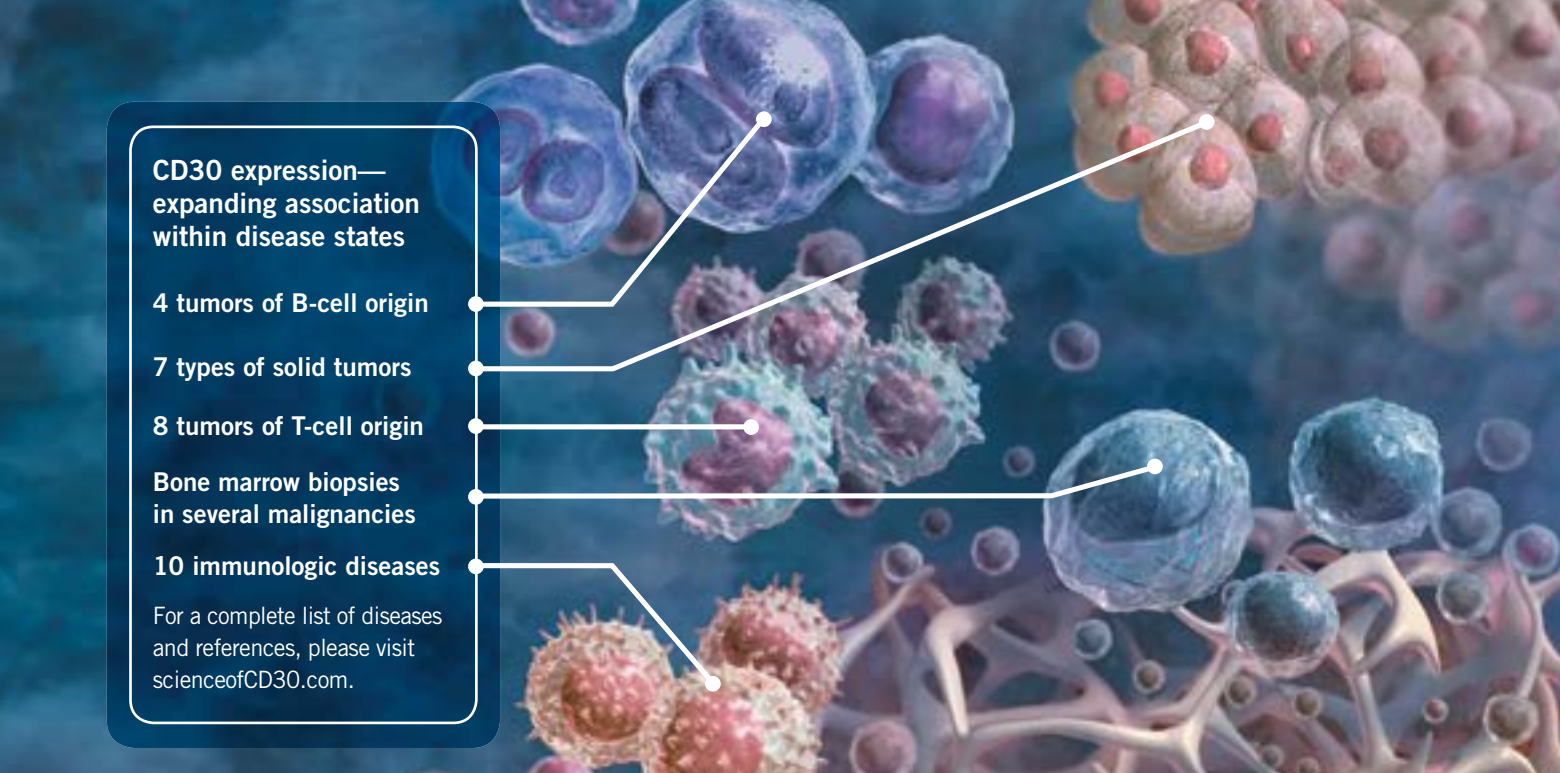
- Brentuximab Vedotin as Single Agent in Refractory or Relapsed CD30-Positive Hodgkin Lymphoma: the French Name Patient Program Experience in 241 Patients
- Subcutaneous Rituximab and Chemotherapy Achieves Similar Overall Response Rates to Intravenous Rituximab in First-Line Follicular Lymphoma: Efficacy and Safety Results of the Phase III SABRINA Study
- Increased Rituximab (R) Doses Eliminate Increased Risk and Improve Outcome of Elderly Male Patients With Aggressive CD20+ B-Cell Lymphomas: the SEXIE-R-CHOP-14 Trial of the DSHNHL
- Phase 3 Study of Frontline Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone Plus Vincristine (R-CHOP) or Bortezomib (VR-CAP) in Transplantation-Unsuitable Mantle Cell Lymphoma (MCL) Patients
- Brentuximab Vedotin for Hodgkin Lymphoma Who Had Failed Allogeneic Stem Cell Transplantation: a Multicenter Retrospective Study
- Final Analysis of a Randomized Phase II Study With Prednisone, Vinblastine, Doxorubicin, and Gemcitabine in Patients With Early Unfavorable Hodgkin Lymphoma-PVAG-14 Pilot
- Preliminary Results of a Phase II Randomized Study (ROMULUS) of Polatuzumab Vedotin or Pinatuzumab Vedotin Plus Rituximab in Patients With Relapsed/Refractory Non-Hodgkin Lymphoma (NHL)
- Phase I Study of ABT-199 (GDC-0199) in Patients With Relapsed/Refractory Non-Hodgkin Lymphoma: Responses Observed in Diffuse Large B-Cell (DLBCL) and Follicular Lymphoma (FL) at Higher Cohort Doses
- Safety and Efficacy of Brentuximab Vedotin (SGN-35) in Hodgkin Lymphoma Patients Undergoing Reduced Intensity Allogeneic Stem Cell Transplant Following a Relapse After Autologous Transplant

PLUS Meeting Abstract Summaries

With Expert Commentary by:

Craig H. Moskowitz, MD
Clinical Director, Division of Hematologic Oncology
Attending Physician, Lymphoma and Adult BMT Services
Member, Memorial Sloan Kettering Cancer Center
Professor of Medicine, Weill Medical College of Cornell University
New York, New York

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**CD30 expression—
expanding association
within disease states**

4 tumors of B-cell origin

7 types of solid tumors

8 tumors of T-cell origin

**Bone marrow biopsies
in several malignancies**

10 immunologic diseases

For a complete list of diseases
and references, please visit
scienceofCD30.com.

CD30: a valuable clinical marker

Diagnosis—the clinical relevance of CD30: Screening for CD30 can assist with the differential diagnosis of CD30-expressing tumors.^{1,2} Immunophenotyping improves diagnostic accuracy by 10% to 45% for a number of major lymphoma subtypes.³ Because of the unique expression characteristics of CD30, diagnostic screening may also assist in the distinction between different types of germ cell tumors.^{4,5}

Prognosis—the prognostic value of CD30: In several types of non-Hodgkin lymphoma, levels of CD30 expression correlate with overall survival (OS). Five-year OS for peripheral T-cell lymphoma, not otherwise specified is 32%, but if $\geq 80\%$ of the cells are CD30-positive, OS is only 19%. Determining CD30 expression can therefore facilitate a risk-adapted approach to treatment.^{2,6-8}

For more information on
CD30 expression, and to
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Brentuximab Vedotin as Single Agent in Refractory or Relapsed CD30-Positive Hodgkin Lymphoma: the French Name Patient Program Experience in 241 Patients

Current treatments fail to cure approximately 20% of patients with Hodgkin lymphoma.¹ For patients with relapsed or refractory Hodgkin lymphoma, the standard of care is salvage chemotherapy followed by autologous stem cell transplantation (SCT), which induces long-term remissions in approximately 50% of patients. For patients who experience relapse after autologous SCT, allogeneic SCT is often a reasonable option. However, effective agents are needed for failure after autograft.

CD30 is a member of the tumor necrosis factor superfamily of transmembrane receptors and is expressed on Hodgkin lymphoma cells. It modulates numerous cellular activities, including cell survival, proliferation, and death. It is expressed on activated T cells, B cells, and natural killer cells. CD30 is not expressed on most normal cells, which makes it an excellent therapeutic target. Brentuximab vedotin is an antibody-drug conjugate that consists of an anti-CD30, immunoglobulin G1 antibody that is conjugated by a protease-cleavable dipeptide linker to the microtubule-disrupting agent monomethyl auristatin E (MMAE).² Binding to CD30 on the cell surface induces drug internalization, which is followed by disruption of the microtubule network, cell cycle arrest, and apoptosis. Brentuximab vedotin was first evaluated as a single agent in 102 patients with relapsed or refractory, CD30-positive leukemia or lymphoma, including 71% with primary refractory disease and 42% with disease that was refractory to the most recent prior therapy.³ The study demonstrated an overall response rate (ORR) of 75%, including a complete response (CR) rate of 34%. Median progression-free

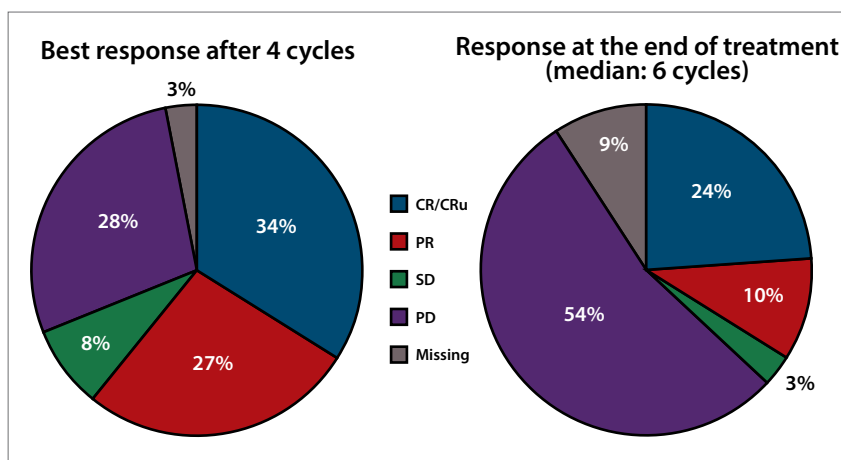


Figure 1. Responses to brentuximab vedotin in a retrospective French trial of patients with relapsed or refractory, CD30-positive Hodgkin lymphoma who failed autologous stem cell transplant or at least 2 prior multiagent chemotherapy regimens, or who were not candidates for autologous stem cell transplant. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; CRu, unconfirmed complete response. Adapted from Perrot A et al. EHA abstract S1293. *Haematologica*. 2014;99(suppl 1):498.⁵

survival (PFS) for the study population was 5.6 months. A long-term update of the phase 2 study showed an estimated 3-year overall survival (OS) of 54%.⁴ This study led to accelerated approval of brentuximab vedotin by the US Food and Drug Administration in 2011.

Starting in January 2011, the French Name Patient Program made brentuximab vedotin available for patients with relapsed or refractory, CD30-positive Hodgkin lymphoma after failure of autologous SCT or after failure of at least 2 prior multiagent chemotherapy regimens in patients who were not candidates for autologous SCT. For the current retrospective study, data were available for 240 patients from 89 French treatment centers who had received brentuximab vedotin (1.8 mg/kg) once every 3 weeks.⁵ The study's primary endpoint was the best response after treatment. Patients had a median age of 30 years, and the cohort was characterized by high-risk

disease: 59% of patients had stage III or IV disease, 59% had received at least 1 transplant, and 16% had received prior allogeneic transplant. The median time to relapse following transplant was 6 months. Patients received a median 6 cycles of antibody therapy, and responses were assessed mainly based on the revised Cheson criteria.⁶

After a median 4 cycles of treatment, the ORR was 61%, including 34% CRs (Figure 1). However, after a median 6 cycles, the response rate decreased, with 24% CRs and 10% partial responses (PRs). Fifty-four percent of patients had progressive disease. In the 140 patients who demonstrated a response, the median duration of response was 8.4 months. After a median follow-up of 16 months, median PFS was slightly longer than 6 months. Median OS was not reached, with an estimated 1-year OS of 76% and 2-year OS of 58%. The drug demonstrated an acceptable toxicity

profile, with no deaths linked to treatment. Grade 1/2 sensory neuropathy was observed in 27% of patients. Diarrhea was reported in 14% of patients. Hematologic toxicities of any grade included anemia (39%), thrombocytopenia (27%), and neutropenia (23%).

A separate study showed that brentuximab vedotin can be safely administered to Hodgkin lymphoma patients who have relapsed after autologous SCT, prior to reduced-intensity conditioning allogeneic SCT. After allogeneic SCT, 7 of 8 study patients remained progression-free after a median follow-up of 12 months.⁷ In the study by Perrot and colleagues, 54 patients who responded to antibody therapy received either autologous SCT (n=27) or allogeneic SCT (n=27).⁵ Median PFS was significantly increased in the patients who received consolidation therapy after treatment with brentuximab vedotin (19 months vs 9 months). The authors concluded that, owing to the short duration of response, transplantation with the intent to cure should be initiated rapidly in relapsed or refractory Hodgkin lymphoma patients who respond to antibody therapy.

Patients with peripheral T-cell lymphoma (PTCL) were also treated through the French Name Patient Program. Outcomes in PTCL patients are generally poor, with a median OS of 6.7 months in patients with relapsed or refractory disease.⁸ Brentuximab vedotin has shown activity in patients with relapsed or refractory anaplastic large cell lymphoma (ALCL), with an ORR of 86% and a CR rate of 57%.⁹ However, although ALCL is characterized by uniformly strong expression of CD30, expression in PTCL tumors is more variable. Data from 66 PTCL patients treated with brentuximab vedotin in the French Name Patient Program were retrospectively analyzed.¹⁰ Eighty-seven percent of patients had Ann Arbor stage III or IV disease, and 39% had primary refractory disease. CD30 expression levels were greater than 75% in 48.8%, 10% to 75% in 30.2%, and undetect-

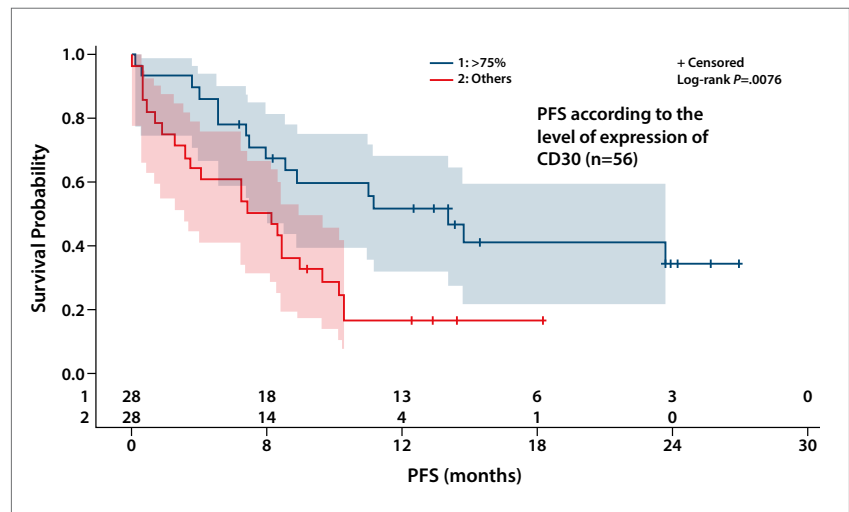


Figure 2. In a French trial of brentuximab vedotin in patients with peripheral T-cell lymphoma, median PFS was longer in patients whose tumors expressed CD30 at levels greater than 75% compared with less than 75%. PFS, progression-free survival. Adapted from Mathilde L et al. EHA abstract P465. *Haematologica*. 2014;99(suppl 1):151.¹⁰

able in 21.0% of tested cases. The 66 patients received a median 5 cycles of brentuximab vedotin, with 11 patients receiving concomitant chemotherapy. Based on Cheson 1999 criteria, CRs were observed in 33 patients (50%), with a median 4 cycles of treatment (range, 1-12) administered prior to the best response.¹¹ At the end of treatment, 30 patients (45%) were still in CR, and 21 (32%) had progressive disease. After a median follow-up of 13.4 months, median duration of response was 13.6 months (95% CI, 4.4 months-not reached), median PFS was 7.3 months (95% CI, 5.2-10.5 months), and median OS was 25.9 months (95% CI, 11.9-not reached). No new toxicities were observed. Median PFS was longer in patients whose tumors expressed CD30 at levels greater than 75% compared with less than 75% ($P=.0076$; Figure 2).

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Subcutaneous Rituximab and Chemotherapy Achieves Similar Overall Response Rates to Intravenous Rituximab in First-Line Follicular Lymphoma: Efficacy and Safety Results of the Phase III SABRINA Study

Rituximab plus chemotherapy followed by rituximab maintenance is standard treatment for follicular lymphoma. Current rituximab formulations are administered intravenously, and often require hours for a single treatment. The availability of a subcutaneous formulation of rituximab that achieves equivalent rituximab serum concentrations would both increase patient convenience and

reduce the costs associated with long infusion times. SABRINA (A Study of MabThera [Rituximab] Subcutaneous Vs. MabThera [Rituximab] Intravenous in Patients With Follicular Non-Hodgkin's Lymphoma) was a 2-stage, phase 3 study designed to demonstrate noninferiority of 3-week cycles of fixed-dose subcutaneous rituximab vs intravenous rituximab. Pharmacokinetic noninferiority was demonstrated

in the first stage of the study based on the subcutaneous:intravenous serum concentration ratio of 1.62 (90% CI, 1.36-1.94).¹ Provisional analysis based on 127 randomized patients demonstrated comparable efficacy. In stage 2, an additional 283 patients were randomized to assess the efficacy and safety of the subcutaneous formulation.² Follicular lymphoma patients received intravenous rituximab plus chemotherapy for the first treatment cycle, then subcutaneous rituximab at 1400 mg or intravenous rituximab at 375 mg/m² plus chemotherapy every 3 weeks for induction cycles 2 through 8, followed by subcutaneous rituximab or intravenous rituximab maintenance every 8 weeks. Chemotherapy consisted of either a maximum of 8 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or 8 cycles of cyclophosphamide, vincristine, and prednisone. Data from 410 patients from stages 1 and 2 were combined for the efficacy and safety analysis. Previously untreated patients with confirmed CD20-positive grade 1, 2, or 3a follicular lymphoma were randomized to receive subcutaneous rituximab or intravenous rituximab. Patients were stratified based on Follicular Lymphoma International Prognostic Index (FLIPI) score, type of chemotherapy, and region. In each arm, approximately two-thirds of patients received CHOP, with the remainder receiving cyclophosphamide, vincristine, and prednisone.

At the end of induction, the investigator-assessed ORR was 83.4% (95% CI, 77.6%-88.2%) for subcutaneous rituximab vs 84.4% (95% CI, 78.7%-89.1%) for intravenous rituximab (Figure 3). Rates of CR,

ABSTRACT SUMMARY Bendamustine-Containing Regimen (BEGEV) Efficiently Mobilizes CD34+ Hematopoietic Cells in Relapsed/Refractory Hodgkin Lymphoma

Although bendamustine monotherapy has shown clinical activity in a variety of lymphoproliferative disorders, including Hodgkin lymphoma, limited data are available regarding its capacity to mobilize peripheral blood stem cells. An ongoing, open-label, prospective, phase 2 study is evaluating the efficacy of bendamustine, gemcitabine, and vinorelbine as induction chemotherapy prior to autologous SCT (Abstract S1294). The study consecutively enrolled 40 patients to receive bendamustine (90 mg/m² on days 2 and 3), gemcitabine (800 mg/m² on days 1 and 4), and vinorelbine (25 mg/m² on day 1) plus granulocyte-colony stimulating factor (10 µg/kg) beginning on day 7 and continuing daily until cell collection, which was targeted at 3 × 10⁶ CD34-positive cells/kg. Peripheral blood stem cell collection was planned after cycle 1 or cycle 3 for patients with bone marrow involvement. Thirty-seven of the enrolled patients underwent peripheral blood stem cell mobilization and harvesting, and 36 achieved the target yield of 3 × 10⁶ CD34-positive cells/kg and were evaluable. Harvesting yielded a median 8.6 × 10⁶ CD34-positive cells/kg (range, 3.6-56 cells/kg) after a median of 1 procedure (range, 1-2 procedures). Median concentrations of precollection CD34-positive cells and white blood cells were 82 cells/µL (range, 22-339 cells/µL) and 24,380 cells/µL (range, 5,400-87,000 cells/µL), respectively. Peripheral blood stem cell collection was performed after a median of 12 days (range, 9-15 days). Leukapheresis was performed in 21 patients at cycle 1, 10 patients after cycle 2, 5 patients after cycle 3, and 1 patient after cycle 4. Grade 1/2 hematologic and nonhematologic AEs were limited, and no toxic deaths occurred. All of the engraftments were successful. The authors concluded that bendamustine had no stem cell toxicity, the bendamustine-containing regimen had high mobilizing capacity, and the mobilized cells retained engraftment potential.

including unconfirmed CR (CRu), were 32.7% for subcutaneous rituximab and 31.7% for intravenous rituximab. After a median follow-up of 14.4 months, adverse events (AEs) were reported in 93% of subcutaneous patients vs 92% of intravenous patients. The majority of AEs were of grade 2 or lower, including 90% of AEs in the subcutaneous arm and 88% of AEs in the intravenous arm. The proportion of patients with at least 1 AE of grade 3 or higher was 49% in the subcutaneous rituximab arm vs 47% in the intravenous rituximab arm, with serious AEs reported in 29% vs 26% of patients, respectively. The most commonly reported serious AEs were infections (10% in the subcutaneous arm vs 8% in the intravenous arm) and neutropenia (6% vs 4%, respectively). Neutropenia and anemia occurred in 5% or fewer patients in each arm. Administration-related reactions were predominantly grade 1 or 2 and occurred in 47% of subcutaneous rituximab patients and 33% of intravenous rituximab patients, with the increase for subcutaneous rituximab patients arising mainly from grade 1 injection site erythema (10% vs 0%).

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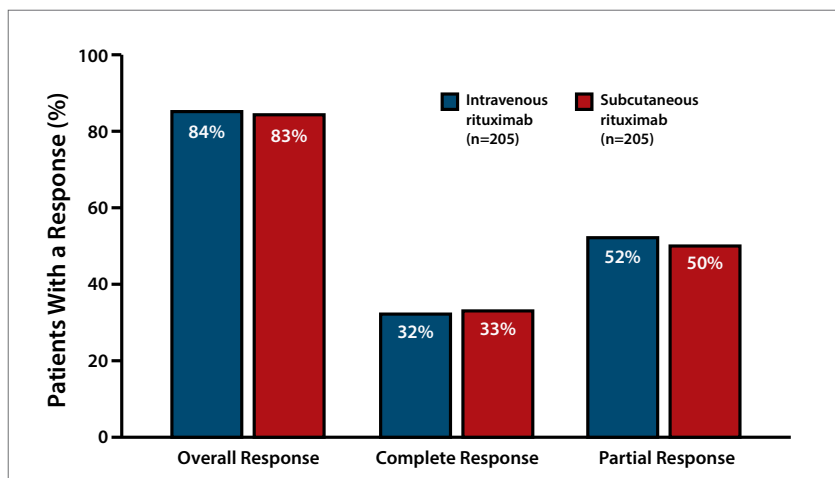


Figure 3. Efficacy results at the end of induction in the SABRINA trial. SABRINA, A Study of MabThera (Rituximab) Subcutaneous Vs. MabThera (Rituximab) Intravenous in Patients With Follicular Non-Hodgkin's Lymphoma. Adapted from Davies A et al. EHA abstract S652. *Haematologica.* 2014;99(suppl 1):225.²

ABSTRACT SUMMARY Targeted BEACOPP Variants in Patients With Newly Diagnosed Advanced Stage Classical Hodgkin Lymphoma: Interim Results of a Randomized Phase II Study

Intensified BEACOPP has substantially improved outcomes for patients with advanced Hodgkin lymphoma, yet the regimen's toxicities—which include severe infections, development of secondary acute myeloid leukemia, infertility, and organ toxicity—are a cause for concern. In order to reduce the regimen's toxicity while retaining efficacy, 2 variants of intensified BEACOPP were examined in a randomized phase 2 study with a planned enrollment of 100 patients (Abstract S1292). In the more conservative variant, bleomycin was omitted and vincristine was replaced by brentuximab vedotin (BrECAPP). The more experimental variant BrECADD incorporated several changes: vincristine was replaced by brentuximab vedotin, procarbazine was replaced with dacarbazine to reduce gonadal toxicity, the dose of etoposide was decreased to reduce the risk of secondary acute myeloid leukemia, the dose of doxorubicin was slightly increased to maintain efficacy, and dexamethasone (on days 1-4) was introduced as a replacement for prednisone (on days 1-14) to avoid immunosuppressive steroid treatment during neutropenia. Both regimens were administered every 21 days for 6 cycles. Outcome data were presented for the first 48 patients. Their median age was 30 years (range, 18-60 years), 57% were male, and 80% had Ann Arbor stage III or IV disease. Forty-six patients had been staged after 6 cycles of chemotherapy, including 24 in the BrECAPP arm and 22 in the BrECADD arm. Forty-one patients (91%) achieved a CR or PET-negative PR. Four patients (9%) had not reached a CR. Sixty-five patients had received at least 2 cycles of chemotherapy and were evaluable for safety analysis. Grade 3/4 organ toxicity occurred in 4 of 31 patients (13%) treated with BrECAPP, and in 0 of 34 patients treated with BrECADD. Thirteen of 46 patients (28%) who had completed treatment showed grade 1 or 2 sensory neurotoxicity (28%).

Increased Rituximab (R) Doses Eliminate Increased Risk and Improve Outcome of Elderly Male Patients With Aggressive CD20+ B-Cell Lymphomas: the SEXIE-R-CHOP-14 Trial of the DSHNHL

The addition of rituximab to CHOP (R-CHOP) has improved outcome in diffuse large B-cell lymphoma (DLBCL).¹ The RICOVER-60 (Combination Chemotherapy With or Without Rituximab in Treating Older Patients With Non-Hodgkin's Lymphoma) trial, conducted by the German High Grade Non-Hodgkin Lymphoma study group, investigated 6 vs 8 cycles of CHOP-14 or R-CHOP-14 in elderly non-Hodgkin lymphoma (NHL) patients.² The study randomized 1222 patients, ages 61 to 80 years, to 1 of the 4 treatment arms. Using 6 cycles of CHOP-14 as the comparator, the other 3 regimens showed improvements in 3-year event-free survival. PFS improved with 6 and 8 cycles of R-CHOP-14 ($P < .0001$ and $P = .0001$, respectively). Improved OS was observed only with 6 cycles of R-CHOP-14 (relative risk, 0.63, 95% CI, 0.38-0.67; $P = .0031$). Multivariate analysis showed an increased risk of progression for male patients compared with female patients who had received rituximab (relative risk, 1.592; $P = .004$), with 4-year PFS rates of 15% for men vs 22% for women. Serum trough levels of rituximab were approximately one-third lower in men, consistent with the increased risk of progression, and pharmacokinetics demonstrated that elderly women have a significantly slower clearance than elderly men, producing higher serum levels and longer exposure times. Extending the pharmacokinetic analysis to younger patients did not reveal significant differences in rituximab clearance based on patient sex. Therefore, elderly men have significantly slower rituximab clearance times than elderly women, younger men, and younger women.

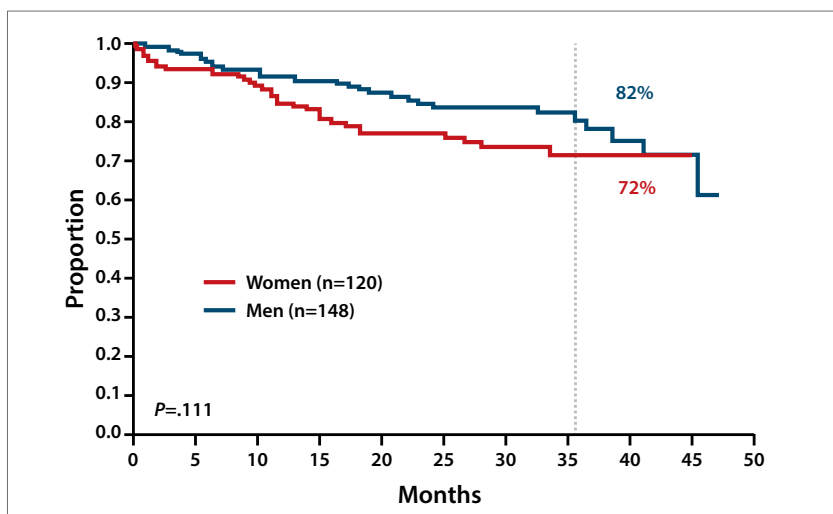


Figure 4. Progression-free survival in the SEXIE-R-CHOP-14 study. Adapted from Pfreundschuh M et al. EHA abstract S1347. *Haematologica*. 2014;99(suppl 1):524.³

Dr Michael Pfreundschuh presented results from the SEXIE-R-CHOP-14 study, which investigated whether an increased dose of rituximab could reduce the hazard for progression in elderly men compared with elderly women.³ The phase 2 trial enrolled patients ages 61 to 80 years with CD20-positive DLBCL. Rituximab was dosed at the standard 375 mg/m² for the 120 women and 500 mg/m² for the 148 men. The female patients had worse prognostic factors, including more advanced disease stage, elevated lactate dehydrogenase, and worse Eastern Cooperative Oncology Group performance status (ECOG PS). Treatment adherence was excellent for both male and female patients, and 98% of all patients received median relative doses of rituximab and myelosuppressive drugs. The target doses of 3000 mg/m² for women and 4000 mg/m² for men were achieved. Men demonstrated a higher serum trough concentration of

rituximab. However, rituximab levels decreased faster in men, and therefore their exposure to the drug was only slightly increased.

The increased dose of rituximab in men was not associated with increased toxicities. Three-year PFS was 74% in men vs 68% in women ($P = .396$), and 3-year OS was 82% vs 72%, respectively ($P = .111$; Figure 4). Multivariate analysis adjusting for International Prognostic Index (IPI) factors showed that the hazard ratio (HR) associated with male sex was 0.9 for PFS ($P = .817$) and 0.8 for OS ($P = .317$). Data from SEXIE-R-CHOP-14 were compared with those from the earlier RICOVER-60 trial² in a multivariate analysis that adjusted for IPI risk factors as well as older age (>70 years). The increased dose in the SEXIE-R-CHOP-14 trial was associated with a reduced risk for an event in PFS (HR, 0.7; $P = .128$) for male patients. The male vs female HR for PFS was 0.8 ($P = .613$) in the SEXIE-R-CHOP-14 trial and

1.6 in RICOVER-60 ($P=.004$). In the SEXIE-R trial, the male vs female HR for OS was 0.7 ($P=.252$) vs 1.4 ($P=.063$) in RICOVER-60. Dr Pfreundschuh concluded that rituximab dosed at 500 mg/m² in men eliminates their increased risk of disease progression or death. Younger patients had unfavorable pharmacokinetics compared with elderly women, and therefore increasing

the rituximab dose in younger male and female patients might also improve outcomes. Moreover, it is possible that the standard dose of 375 mg/m² in elderly women is suboptimal.

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Phase 3 Study of Frontline Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone Plus Vincristine (R-CHOP) or Bortezomib (VR-CAP) in Transplantation-Unsuitable Mantle Cell Lymphoma (MCL) Patients

Mantle cell lymphoma (MCL), an aggressive type of NHL, is currently incurable. Standard first-line therapy, such as R-CHOP, results in limited PFS rates in patients with newly diagnosed disease. Bortezomib is approved for relapsed MCL and could improve outcomes if incorporated into first-line therapy. Dr Tadeusz Robak presented the primary analysis of a study investigating whether using bortezomib in place of vincristine in R-CHOP therapy could improve outcomes in newly diagnosed MCL patients who are unsuitable for bone marrow transplantation.¹ The study was performed at 128 centers in 22 countries throughout Europe, North America, South America, and Asia. Eligible patients had stage II to IV disease and an ECOG PS of 0 to 2. Diagnosis was performed locally and confirmed at a central laboratory; the concordance rate was 97%. After stratification based on IPI score and disease stage, patients were evenly randomized to receive a minimum of six 21-day cycles of rituximab (375 mg/m²), cyclophosphamide (750 mg/m²), doxorubicin (50 mg/m²) on day 1, and prednisone (100 mg/m²) on days 1 through 5, plus either intravenous bortezomib (1.3 mg/m²) on days 1, 4, 8, and 11 (VR-CAP) or intravenous vincristine

ABSTRACT SUMMARY Management of Relapsed/Refractory Lymphoma With Brentuximab Vedotin: Our Experience in the Treatment of Young Patients

A publication-only abstract described the successful use of brentuximab vedotin to treat 3 lymphoma patients who had experienced several relapses (Abstract PB1859). The first case involved a 21-year-old man diagnosed with systemic, stage IIIB, non-B-cell, non-T-cell ALCL that was positive for anaplastic lymphoma kinase and CD30. In November 2011, he underwent 6 cycles of first-line CHOP and experienced a CR. He then underwent chemotherapy with ifosfamide, epirubicin, and etoposide, but his disease relapsed after 2 courses. His treatment was switched to dexamethasone, cytarabine, and cisplatin, with an apparent improvement, but his condition worsened 1 month after the first course. At this point, the patient was switched to brentuximab vedotin (1.8 mg/kg). After the first course, the patient experienced a severe respiratory reaction; this reaction was addressed, and antibody treatment resumed. The treatment was well tolerated thereafter, and after 6 courses, the patient was in CR. In November 2013, he underwent allogeneic SCT, and after 4 months, he showed no signs of disease. The second case was a 35-year-old woman diagnosed in February 2011 with classic nodular sclerosis Hodgkin lymphoma, stage IIB with mediastinal bulky disease. After her second disease progression, she received 3 courses of chemotherapy followed by autologous SCT in September 2012. Progressive disease was again documented in February 2013. Brentuximab vedotin (1.8 mg/kg) was initiated, and the patient experienced a CR after 12 courses. The only documented side effect was alopecia. The third case was a 30-year-old woman diagnosed in April 2004 with classic nodular sclerosis Hodgkin lymphoma, stage IIB, with splenic localization. The patient relapsed 3 times on different chemotherapy regimens, the last of which was dexamethasone, cytarabine, and cisplatin plus rituximab. In October 2009, the patient started rituximab maintenance that was continued until July 2012, when progressive disease was documented. At this point, the patient's overall condition had deteriorated to the point that she could no longer walk. She initiated treatment with brentuximab (1.8 mg/kg) and experienced a CR after 6 courses. The only side effect was grade 1 neuropathy.

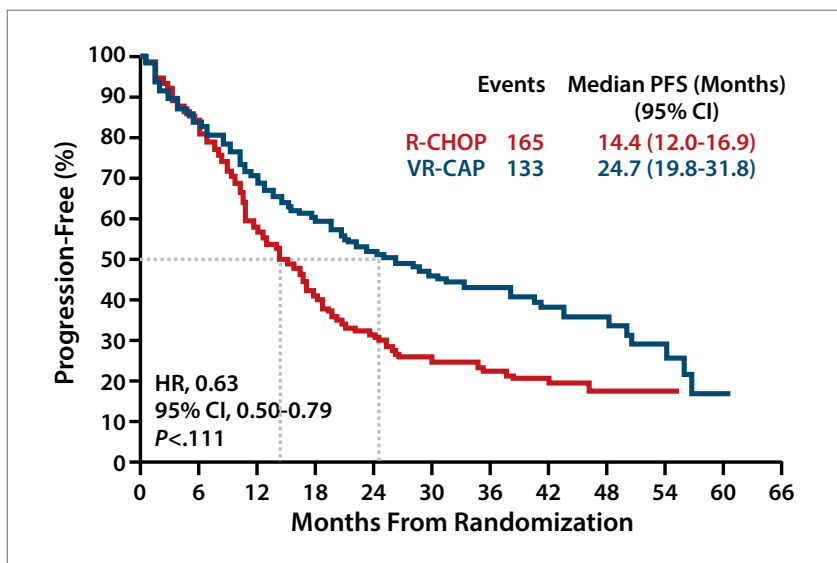


Figure 5. PFS in patients with mantle cell lymphoma who received R-CHOP or a variant that replaced vincristine with bortezomib. HR, hazard ratio; PFS, progression-free survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; VR-CAP, rituximab plus cyclophosphamide, doxorubicin, prednisone, and bortezomib. Adapted from Robak T et al. EHA abstract S1345. *Haematologica*. 2014;99(suppl 1):523.¹

ABSTRACT SUMMARY Impact of Bleomycin and Dacarbazine Within the ABVD Regimen in the Treatment of Early-Stage Favorable Hodgkin Lymphoma: Final Results of the GHSG HD13 Trial

Combined modality treatment consisting of 2 cycles of ABVD followed by involved-field radiotherapy is a standard of care for early-stage, favorable Hodgkin lymphoma. To determine the impact of bleomycin and dacarbazine within the ABVD regimen, study HD13 from the GHSG compared ABVD with 3 variant regimens lacking dacarbazine (ABV), bleomycin (AVD), or both (AV). In all arms, treatment consisted of 2 cycles of chemotherapy followed by 30 Gy involved-field radiotherapy (Abstract S1290). The primary objective was to demonstrate noninferiority of the 3 experimental variants compared with ABVD based on the primary endpoint of freedom from treatment failure and a predefined noninferiority margin of 6% after 5 years. Recruitment started in January 2003. Owing to higher AE rates, the AV and ABV arms were closed early. Among the 1502 qualified patients analyzed for therapy adherence, toxicity, and efficacy, 566 were randomized into the ABVD arm and 198, 571, and 167 patients were randomized to receive experimental chemotherapy with ABV, AVD, or AV, respectively. Patient characteristics were well balanced among the 4 treatment arms. The median age was 39 years, 67% had stage II disease, and 60% were male. The rate of acute toxicities ranged from 26.3% with AVD to 32.7% with ABVD, with leukopenia (14.4%), hair loss (10.9%), and nausea/vomiting (5.8%) most frequently observed. The omission of bleomycin or dacarbazine resulted in only a slight decrease in toxicities. At 5 years, freedom from treatment failure was 93.1% for ABVD, and the 2 arms that were closed early showed inferiority, with rates of freedom from treatment failure of 81.4% for ABV and 77.1% for AV. The noninferiority of AVD, which showed a 5-year freedom from treatment failure of 89.2%, was not confirmed (HR, 1.5; 95% CI, 1.0-2.3). OS did not significantly differ among the treatment arms, at 97.6% for ABVD, 94.1% for ABV, 97.6% for AVD, and 98.1% for AV.

(1.4 mg/m²) on day 1 (R-CHOP). For patients with a confirmed response following the sixth treatment cycle, 2 additional courses of treatment were allowed. The study's primary endpoint was PFS by independent radiology review. Secondary endpoints included ORR, CR, OS, time to response, and response duration. The most important statistical assumption was a 40% improvement in the duration of PFS, from 18 months for R-CHOP to 25 months for VR-CAP. The design required 295 events to provide 80% power to detect such an improvement. Two interim safety analyses, plus a final analysis for safety and efficacy, were planned.

The study randomized 487 patients evenly into the 2 treatment arms, which were well balanced for demographics and baseline characteristics. Patients had a median age of 66 years, and approximately three-fourths were male. Seventy-four percent of patients had stage IV MCL, and 54% had an IPI score of at least 3. The majority of patients received at least 6 courses of treatment, with 17% of R-CHOP and 13% of VR-CAP patients receiving 8 courses by protocol. Treatment was completed by 82% of patients in the R-CHOP arm and 80% of patients in the VR-CAP arm. The majority of patients received all planned doses of rituximab, cyclophosphamide, doxorubicin, and prednisone. The analysis was predicated on the occurrence of 165 events in the R-CHOP arm and 133 events in the VR-CAP arm. After a median follow-up of 40 months, PFS was 14.4 months for patients treated with R-CHOP and 24.7 months for patients treated with VR-CAP (HR, 0.63; $P < .001$; Figure 5). A similar difference was observed based on investigator evaluations (16.1 months for R-CHOP vs 30.7 months for VR-CAP; HR, 0.51; $P < .001$). A subgroup analysis showed that the only patients who did not benefit from VR-CAP were from North America; however, this group included only 14 patients. Median time to progression

as assessed by independent review was 16.1 months for the R-CHOP arm vs 30.5 months for the VR-CAP arm (HR, 0.58; $P < .001$).

VR-CAP induced a higher rate of CR plus CRu (53% vs 42%; odds ratio, 1.7; $P = .007$), although the ORR was similar in both arms (92% with VR-CAP vs 90% with R-CHOP; odds ratio, 1.4; $P = .275$). Median OS was 56.3 months for patients treated with R-CHOP and had not been reached for the experimental arm (HR, 0.80; $P = .17$). Median time to response was shorter with VR-CAP (1.4 months vs 1.6 months), and the duration of CR was 24 months longer in patients treated with VR-CAP. Four-year OS was 64.4% for patients treated with VR-CAP vs 53.9% with R-CHOP. The majority of deaths occurred from progressive disease (23% of patients in the R-CHOP arm and 18% in the VR-CAP arm). In each arm, 7% of patients died from AEs. Grade 3 or higher AEs occurred in 85% of R-CHOP patients vs 93% of VR-CAP patients. AEs observed in at least 10% of patients in either arm included neutropenia (67% with R-CHOP vs 85% with VR-CAP), leukopenia (29% vs 44%), thrombocytopenia (6% vs 57%), lymphopenia (9% vs 28%), anemia (14% vs 15%), and febrile neutropenia (14% vs 15%). Despite the difference in thrombocytopenia rates in the 2 arms, the rates of bleeding events were similar. Peripheral neuropathy of any grade occurred in 29% of R-CHOP patients vs 30% of VR-CAP patients, with grade 3 or higher peripheral neuropathy occurring in 4% of R-CHOP patients vs 8% of VR-CAP patients. However, time to

onset was longer and events showed earlier improvement in patients who received VR-CAP. Serious AEs occurred in 30% of the R-CHOP arm vs 38% of the VR-CAP arm. There were similar rates of treatment discontinuation owing to AEs (7% in the R-CHOP arm vs 9% in the VR-CAP arm) and mortality from drug-related deaths while on

treatment (3% vs 2%). A final analysis of OS data is expected in June 2017.

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ABSTRACT SUMMARY The Addition of Rituximab to CODOX-M/IVAC Chemotherapy in the Treatment of Burkitt Lymphoma Is Safe and Is Associated With Increased Efficacy in the HIV Positive Population

Burkitt lymphoma, a rare, aggressive type of NHL, is one of the most common lymphomas in patients with human immunodeficiency virus (HIV) infection. Treatment typically consists of short, intensive chemotherapy regimens. Rituximab is not routinely included in treatment owing to fears of increased toxicity, despite its ability to improve survival in HIV-negative patients. A retrospective study was therefore conducted to evaluate the safety and efficacy of cyclophosphamide, doxorubicin, and high-dose methotrexate alternating with ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC) chemotherapy with or without rituximab in HIV-positive patients (Abstract P460). Ninety-one patients with HIV-related Burkitt lymphoma received treatment at 5 London centers between 2003 and 2013. Forty-nine patients received CODOX-M/IVAC, and 42 patients received CODOX-M/R-IVAC, which included a median of 6 doses of rituximab. Although 87% of patients received intravenous antibiotics, opportunistic infections were infrequent. In the rituximab group, fungal chest infections were suspected in 1 patient and confirmed in 2 patients. Three patients who received rituximab plus chemotherapy and 2 patients who received chemotherapy alone experienced cytomegalovirus reactivation requiring treatment. The addition of rituximab yielded no significant increase in bone marrow suppression, nor was there any significant increase in grade 3/4 toxicity, including infections, mucositis, diarrhea, renal impairment, and tumor lysis syndrome. After a median follow-up of 41 months (range, 3-109 months), 2-year OS was 68% for the entire study population and was improved in patients who received rituximab (72% [95% CI, 0.22-0.92; HR, 0.46] vs 55% [95% CI, 1.1-4.5; HR, 2.2]; $P = .04$). Death from sepsis was reported in 4 patients who received chemotherapy alone and 2 patients who received chemotherapy plus rituximab. No significant differences emerged in the incidence of toxic deaths or disease relapse between the 2 treatment groups.

Brentuximab Vedotin for Hodgkin Lymphoma Who Had Failed Allogeneic Stem Cell Transplantation: a Multicenter Retrospective Study

Approximately 50% of Hodgkin lymphoma patients relapse following allogeneic SCT.¹ Limited treatment options are available for these patients, and only about half survive to 3 years. Brentuximab vedotin has shown encouraging results in early phase 1 and 2 trials in this patient population. In a study of 25 Hodgkin lymphoma patients who relapsed after allogeneic SCT, treatment with brentuximab vedotin (1.2 mg/kg or 1.8 mg/kg) every 3 weeks yielded an ORR of 50% and a CR rate of 38%.² Median PFS was 7.8 months, and the median OS was not reached.

To further investigate the use of brentuximab vedotin in relapsed Hodgkin lymphoma patients, a multicenter,

retrospective analysis examined safety and efficacy outcomes in 16 heavily pretreated patients with CD30-positive Hodgkin lymphoma who progressed following allogeneic SCT.³ Patients were treated at 4 institutions in a compassionate-use program from June 2011 to January 2014 and received brentuximab vedotin monotherapy (1.8 mg/kg) every 3 weeks. Patients had a median age of 29 years (range, 22-43 years), and 81% were male. Two patients (12.5%) had an ECOG PS of 2 or higher, 6 (37.5%) had B symptoms, 3 (18.7%) had bulky disease, and 12 (75%) had Ann Arbor stage IV disease. Patients had received a median of 8 prior regimens (range, 4-15), and 5 patients (31%) were refractory to their

first line of therapy. The best response was achieved after a median of 4 cycles (range, 2-12 cycles; Figure 6). The median duration of treatment was 6 months (range, 2-10.5 months).

After a median follow-up of 26 months, the ORR was 69%, including 5 patients with CRs and 5 with PRs. In patients who achieved a CR, the response persisted for a median 4 months (range, 3-24+ months) from study drug discontinuation. Of these 5 patients, 1 received a haploidentical allotransplant, 1 received a donor lymphocyte infusion, and the remaining 3 did not receive further treatment after discontinuing the study drug. The 5 patients who achieved a PR experienced progressive disease after a median of 8 cycles (range, 5-17 cycles),

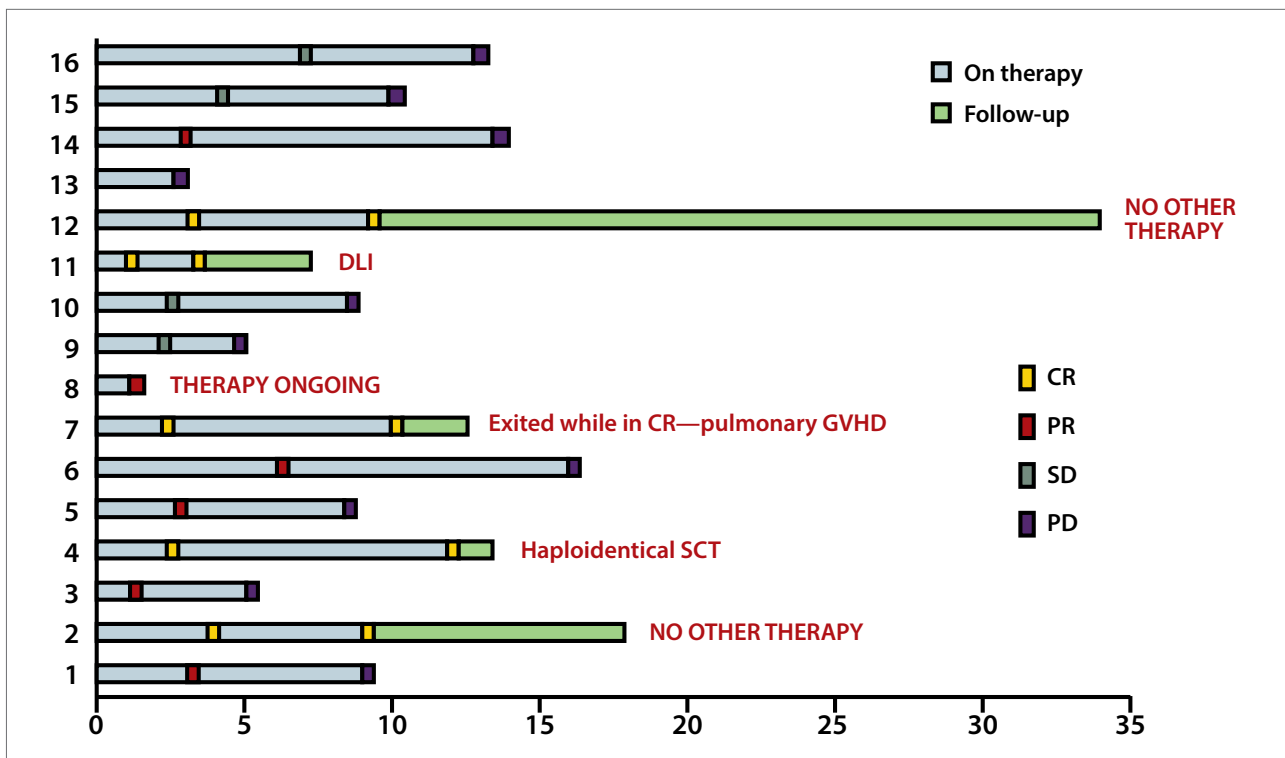
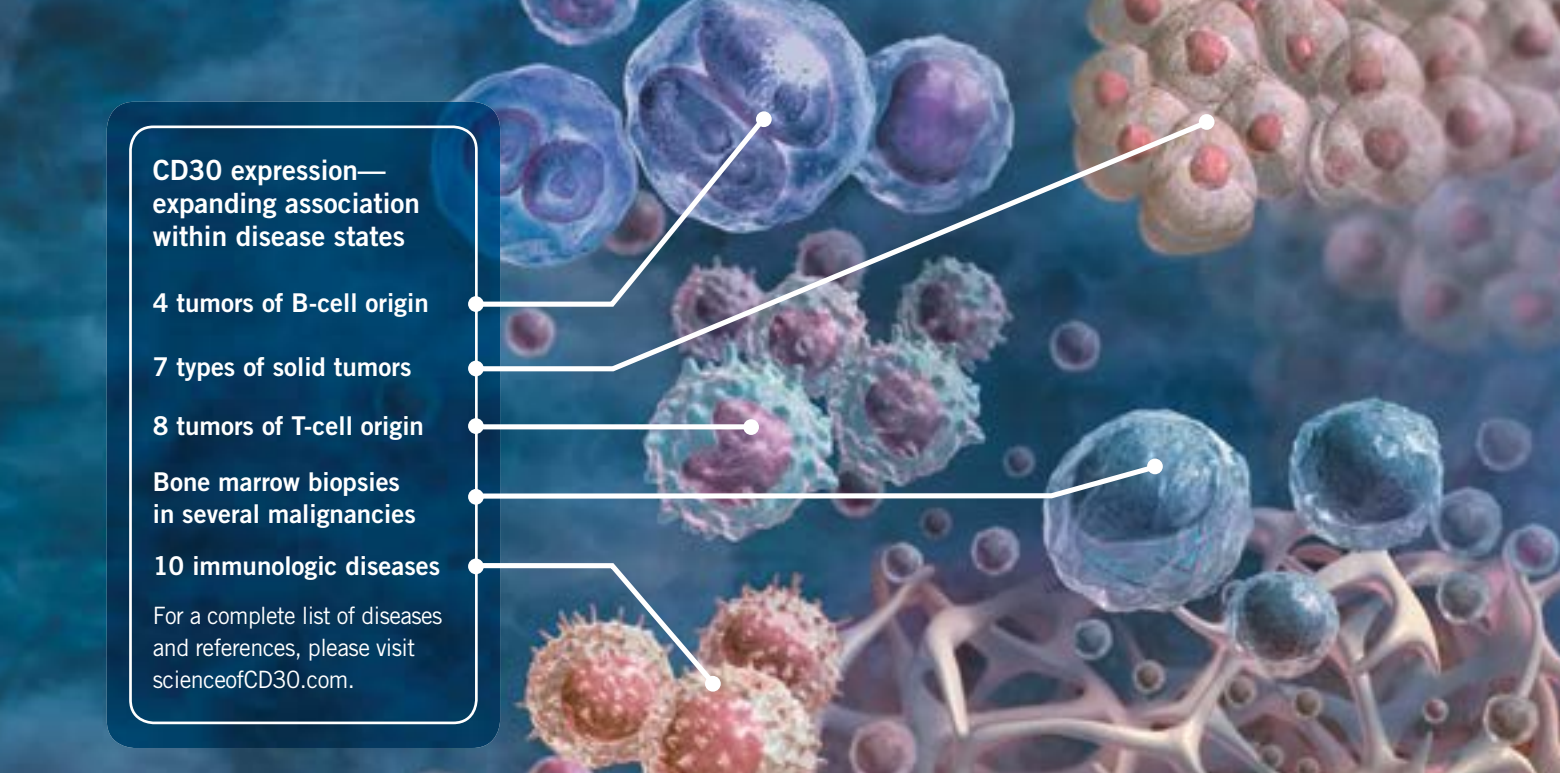


Figure 6. Best response and duration of response in a study of brentuximab vedotin in relapsed Hodgkin lymphoma. CR, complete response; DLI, donor lymphocyte infusion; GVHD, graft-vs-host disease; PD, progressive disease; PR, partial response; SCT, stem cell transplant; SD, stable disease. Adapted from Ricci F et al. EHA abstract P1054. *Haematologica*. 2014;99(suppl 1):402.³



**CD30 expression—
expanding association
within disease states**

4 tumors of B-cell origin

7 types of solid tumors

8 tumors of T-cell origin

**Bone marrow biopsies
in several malignancies**

10 immunologic diseases

For a complete list of diseases
and references, please visit
scienceofCD30.com.

CD30: a valuable clinical marker

Diagnosis—the clinical relevance of CD30: Screening for CD30 can assist with the differential diagnosis of CD30-expressing tumors.^{1,2} Immunophenotyping improves diagnostic accuracy by 10% to 45% for a number of major lymphoma subtypes.³ Because of the unique expression characteristics of CD30, diagnostic screening may also assist in the distinction between different types of germ cell tumors.^{4,5}

Prognosis—the prognostic value of CD30: In several types of non-Hodgkin lymphoma, levels of CD30 expression correlate with overall survival (OS). Five-year OS for peripheral T-cell lymphoma, not otherwise specified is 32%, but if $\geq 80\%$ of the cells are CD30-positive, OS is only 19%. Determining CD30 expression can therefore facilitate a risk-adapted approach to treatment.^{2,6-8}

For more information on
CD30 expression, and to
download an educational
presentation on CD30,
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and patients who achieved stable disease progressed after a median of 3 months (range, 2-6 months). Median PFS was 10.6 months, and median OS was 25.2 months. At 2 years, PFS was 22% and OS was 48%.

At the most recent follow-up, 10 patients (62.5%) were alive, and 4 were in continuous CR. Among the patients who died, the cause of death was progressive disease in 5 patients and pulmonary graft-vs-host disease in 1 patient while in CR. The most com-

mon AEs included peripheral neuropathy of grade 1 (3 patients) or grade 3 (1 patient). Two patients developed infections with gram-positive bacteria, and 2 patients developed fever of unknown origin. One patient developed Guillain-Barré syndrome. Brentuximab vedotin was associated with a high rate of disease control in this study. However, based on the short duration of responses, the authors concluded that brentuximab vedotin should be investigated in combination with other agents, such as che-

motherapy, to improve disease control and increase the ORR.

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Final Analysis of a Randomized Phase II Study With Prednisone, Vinblastine, Doxorubicin, and Gemcitabine in Patients With Early Unfavorable Hodgkin Lymphoma-PVAG-14 Pilot

Optimal treatment for patients with early-stage, unfavorable Hodgkin lymphoma remains undefined. These patients often receive "2+2" chemotherapy, which consists of 2 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by 2 cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) chemotherapy. However, this approach is accompanied by high rates of toxicity, and efficacy is limited, with a 5-year PFS of 6% even with intensified regimens.¹ Moreover, increasing the number of treatment cycles does not improve outcomes. Because gemcitabine has shown promising activity in relapsed NHL, the German Hodgkin Study Group tested a new chemotherapy regimen with gemcitabine in the phase 2 PVAG-14 trial.² The trial planned to enroll 50 patients with their first diagnosis of stage I or II, unfavorable Hodgkin lymphoma, based on German Hodgkin Study Group criteria.³ Patients received 8 cycles of PVAG-14 and were randomized to receive 1 of 2 doses of doxorubicin. PVAG-14 con-

Table 1. PVAG in Early Unfavorable Hodgkin Lymphoma

	8 × PVAG-14 D=25 mg/m ² n=21 (%)	8 × PVAG-14 D=35 mg/m ² n=20 (%)	All Patients n=41 (%)
CR	24	35	29
CRu	67	65	66
PR	5		2
Missing	5*		2*
CR/CRu	90	100	95

ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; CR, complete response; CRu, complete response, unconfirmed; D, doxorubicin; PR, partial response; PVAG, prednisone, vinblastine, doxorubicin, and gemcitabine.

*One patient received ABVD after discontinuation of PVAG-14 and achieved a CR.

Data from Fuchs M et al. EHA abstract S1291. *Haematologica*. 2014;99(suppl 1):497.²

sisted of prednisone (50 mg on days 1-3), vinblastine (6 mg/m² on day 1), doxorubicin (25 or 35 mg/m² on day 1), and gemcitabine (1000 mg/m² on day 1), followed by 30 Gy of involved-field radiotherapy. Patients also received pegfilgrastim (6 mg on day 2). The primary objectives were to assess the toxicity and efficacy of the PVAG-14 regimen, with the goal of achieving a toxicity rate of less than 50% and a CR rate of greater than 50%.

The trial recruited 41 patients between November 2008 and May

2011, but it was closed early owing to poor recruitment likely caused by the start of another trial with a similar patient population. Patients had a median age of 38 years (range, 18-57 years), and 17% of the patients were older than 50 years. Forty-nine percent of the patients were male. Approximately three-fourths of patients had stage IIA disease, and the same proportion had a World Health Organization activity index of 0. Approximately 20% of patients had a large mediastinal mass, more than 60% had at least 3 involved nodal areas, and 51%

had a high erythrocyte sedimentation rate. All but 1 patient received 8 cycles of PVAG-14, with a median dose intensity of 97%. Sixty-six percent of the patients received granulocyte-colony stimulating factor with each cycle, according to protocol. One patient discontinued chemotherapy after 3 cycles owing to intolerance to granulocyte-colony stimulating factor and eventually switched to ABVD therapy. Grade 3/4 hematologic toxicity was observed in 9.8% of the entire study population, in 4.8% of the patients receiving the lower dose of doxorubicin, and in 15% of those receiving the higher dose of doxorubicin. The most common grade 3/4 toxicity was leukopenia, occurring in 9.8% of patients. Three patients had grade 3 leukopenia, and 1 patient had grade 4 leukopenia. No treatment-related anemia or thrombocytopenia

was reported. Grade 3 infections were observed in 7.3% of patients, with no grade 4 infections reported. Skin toxicity was observed in 7.3% of patients. Overall, 37% of patients exhibited a grade 3 or 4 hematologic or nonhematologic toxicity.

The CR rate was 95%, fulfilling an aim of the study (Table 1). For the 20 patients receiving doxorubicin at the higher dose, 35% demonstrated a CR and 65% demonstrated a CRu. Disease progression occurred in 2 patients after the end of therapy (1 at 5 months and 1 at 15 months); 1 of these patients eventually experienced a second relapse and death from Hodgkin lymphoma 27 months after the initial diagnosis. The 2-year OS was 94.4% (95% CI, 67%-99%), with 2-year PFS of 94.3% (95% CI, 79%-99%). Comparison of

outcomes based on the 2 different doxorubicin doses was not performed owing to the low numbers of patients in each arm. The study suggested that PVAG-14 is safe and effective in patients with early-stage, unfavorable Hodgkin lymphoma, demonstrating a high rate of CRs and a low rate of grade 3/4 toxicities.

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Preliminary Results of a Phase II Randomized Study (ROMULUS) of Polatuzumab Vedotin or Pinatuzumab Vedotin Plus Rituximab in Patients With Relapsed/Refractory Non-Hodgkin Lymphoma (NHL)

Pinatuzumab vedotin and polatuzumab vedotin are novel antibody-drug conjugates. Like brentuximab vedotin, these constructs consist of an MMAE tubulin inhibitor conjugated to an antibody with a cleavable peptide linker. Pinatuzumab vedotin binds to CD22, and polatuzumab vedotin binds to CD79b. Both agents ultimately induce apoptosis in targeted cells.^{1,2} These agents have demonstrated efficacy with acceptable toxicity in patients with relapsed or refractory B-cell NHL.^{3,4} The recommended phase 2 dose is 2.4 mg/kg every 3 weeks for up to 1 year, and the main dose-limiting toxicity is neutropenia. The efficacy and safety of each of these antibody-drug conjugates was evaluated in combination with rituximab in the ROMULUS (A Study of DCDT2980S in Combination With MabThera/Rituxan or DCDS4501A in

Combination With MabThera/Rituxan in Patients With Non-Hodgkin's Lymphoma) trial.⁵ This phase 2 trial enrolled 41 patients with relapsed or refractory follicular lymphoma and 81 patients with relapsed or refractory DLBCL. Patients were evenly randomized to receive rituximab (375 mg/m²) plus either pinatuzumab vedotin (2.4 mg/kg) or polatuzumab vedotin (2.4 mg/kg) in 21-day cycles. Rituximab was administered prior to the other agent during the first 2 cycles and then given in combination for subsequent cycles. Patients with progressive disease and those who showed no response to treatment were allowed to switch to the other arm. Treatment-emergent AEs were evaluated based on National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Antitumor activity was evaluated based on revised

International Working Group criteria every 3 months, with positron emission tomography (PET) performed at the physician's discretion.⁶ Pharmacokinetic and pharmacodynamic evaluations included level of total antibody, drug conjugate, and unconjugated MMAE.

The study population was heavily pretreated and had poor-risk features, with the DLBCL patients showing a slightly worse risk profile. Approximately half of the patients were refractory to rituximab, and 80% of the DLBCL patients were refractory to their most recent treatment. The DLBCL patients had received a median of 3 prior therapies (range, 1-10), and the follicular lymphoma patients had received a median of 2 prior therapies (range, 1-8). The DLBCL patients received a median of 6 to 7 treatment cycles for the 2 regimens, and the median time of study

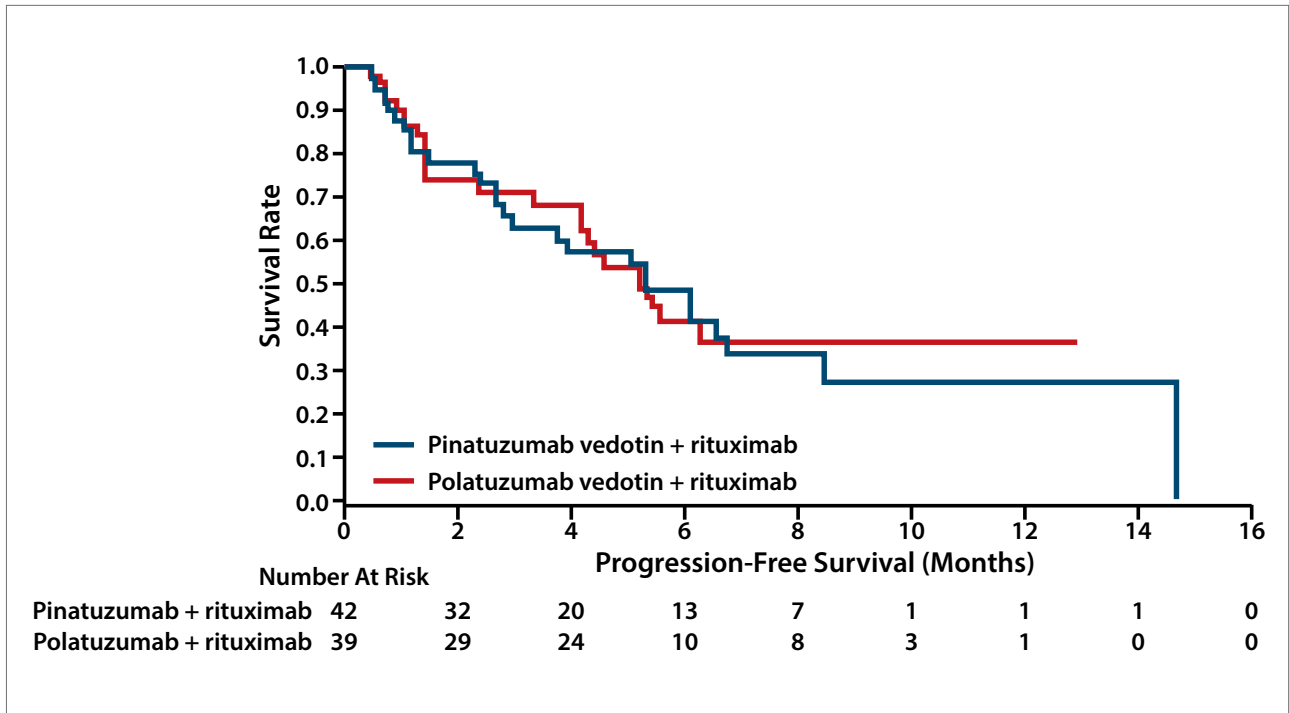


Figure 7. Progression-free survival in DLBCL patients who received treatment with pinatuzumab vedotin or polatuzumab vedotin. DLBCL, diffuse large B-cell lymphoma. Adapted from Morschhauser F et al. EHA abstract S1349. *Haematologica*. 2014;99(suppl 1):525.⁵

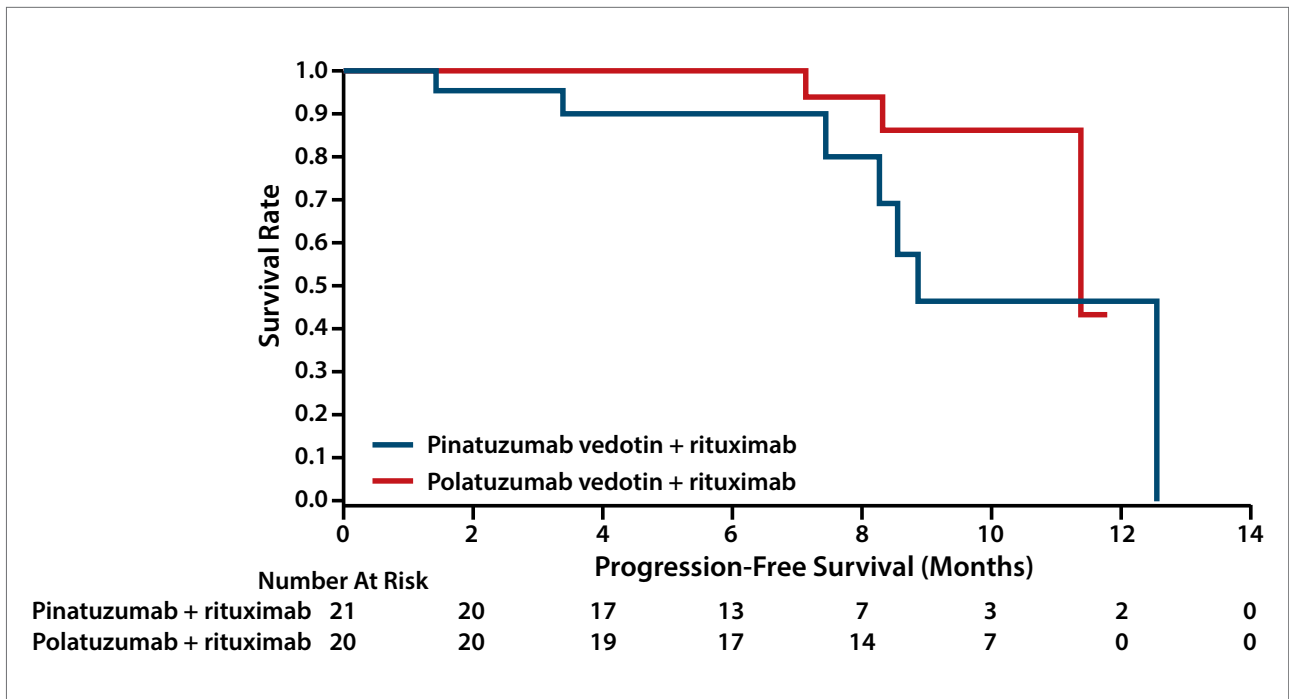


Figure 8. Progression-free survival in follicular lymphoma patients who received treatment with pinatuzumab vedotin or polatuzumab vedotin. Adapted from Morschhauser F et al. EHA abstract S1349. *Haematologica*. 2014;99(suppl 1):525.⁵

treatment was approximately 4 months. One-third of patients discontinued owing to AEs. The follicular lymphoma patients received approximately 10 treatment cycles of polatuzumab and 7 cycles of pinatuzumab, and they remained on treatment for approximately 7 months. Two-thirds of the follicular lymphoma patients discontinued treatment owing to AEs, possibly because these patients had less aggressive disease characteristics.

The 2 regimens showed similar overall safety profiles. The most common treatment-emergent AEs of any grade included fatigue (52%), diarrhea (42%), and nausea (37%). AEs of grade 3 or higher occurring in at least 3% of patients included neutropenia (21%), diarrhea (6%), dyspnea (4%), febrile neutropenia (4%), hyperglycemia (4%), and peripheral neuropathy (4%). Serious AEs were observed in 36% of patients. Although neutropenia was the most significant grade 3/4 toxicity, the clinical consequences were limited; only 1 patient discontinued treatment owing to febrile neutropenia. Approximately one-third of the patients received granulocyte-colony stimulating factor, either as prophylaxis or as an intervention for neutropenia. Peripheral neuropathy was clinically significant in this study, as it was in the earlier phase 1 studies. Approximately half of the patients had a history of peripheral neuropathy at baseline, largely caused by prior therapy, and one-third of the patients had ongoing grade 1 peripheral neuropathy at baseline. Half of the patients in the DLBCL cohort experienced peripheral neuropathy, with one-third experiencing neuropathy of grade 2 or higher. Peripheral neuropathy was common in the follicular lymphoma cohort, occurring in approximately 80% of patients in the pinatuzumab arm and 100% of patients in the polatuzumab arm. With the increasing treatment duration, up to 80% of patients experienced peripheral neuropathy of grade 2 or higher. The median time of onset for peripheral neuropathy was 3 months, or approximately 4 treatment cycles, and the median time to onset of grade

ABSTRACT SUMMARY High Doses of Antimetabolites Followed by High-Dose Sequential Chemoimmunotherapy and Autologous Stem Cell Transplant in Systemic B-Cell Lymphomas With CNS Involvement: a Multicenter Phase II Trial

A phase 2 trial was conducted to address the feasibility of a new, intensified chemoimmunotherapy that includes high doses of antimetabolites with subsequent autologous SCT in patients with B-cell lymphomas and secondary central nervous system involvement (Abstract P472). The trial enrolled 39 HIV-negative patients with systemic B-cell lymphoma and central nervous system disease at diagnosis or relapse. Patients received 2 cycles of methotrexate, cytarabine, and rituximab, 1 cycle of cyclophosphamide, rituximab, and cytarabine, and 1 cycle of cytarabine plus rituximab. Patients with residual disease also received etoposide plus liposomal cytarabine. The treatment included 8 doses of rituximab and 4 doses of intrathecal liposomal cytarabine. The 39 patients had a median age of 54 years (range, 32-70 years), and 31% had an ECOG PS greater than 1. Fifty-nine percent of patients had relapsed disease, 84% had DLBCL, and more than half had brain parenchyma involvement. The most common grade 4 AEs included neutropenia (90%), thrombocytopenia (76%), and febrile neutropenia (26%). The only reported grade 4 nonhematologic toxicities were transient increase in transaminase levels in 2 patients and 1 incident of intestinal perforation. Opportunistic infections occurred in 7 patients and were successfully managed. Four deaths from AEs were recorded, including 2 from sepsis and 2 from stroke. The ORR was 61% and included 59% CRs and 3% PRs. Peripheral blood stem cells were successfully collected in 23 of 25 patients, and 20 patients underwent autologous SCT. After a median follow-up of 3 years, 2-year PFS was 40%±8%. Overall, 2-year OS was 41%±8%. Among patients who had undergone autologous SCT, it was 64%±11%. ORR, PFS, and OS were similar in patients treated at diagnosis vs relapse, as well as in patients with parenchymal vs meningeal disease.

2 or higher peripheral neuropathy was approximately 6 months, or 8 cycles. The study protocol specified mitigation of peripheral neuropathy to grade 1 severity or baseline by dose delay, followed by dose reduction to 1.8 mg/kg. Although approximately half of the patients recovered, the recovery was not to baseline in most patients. The addition of rituximab added no meaningful benefit to the pharmacokinetic profile of either study drug. No free MMAE accumulation was observed.

After a median follow-up of 9.9 months, the DLBCL patients showed an ORR of 57% with pinatuzumab and 56% with polatuzumab. The CR rate was 24% with pinatuzumab and 15% with polatuzumab, with overlapping confidence intervals. The median duration of response was 6 months for pinatuzumab and was not reached for polatuzumab. The follicular lymphoma

patients showed an ORR of 62% with pinatuzumab and 70% with polatuzumab. The CR rates for follicular lymphoma patients were 10% with pinatuzumab and 40% with polatuzumab. Again, the median duration of response was approximately 6 months for pinatuzumab but was not reached with polatuzumab. Median PFS was approximately 5 months for DLBCL patients treated with either regimen (Figure 7). Median PFS for the follicular lymphoma patients was not reported, owing to insufficient follow-up (Figure 8).

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Phase I Study of ABT-199 (GDC-0199) in Patients With Relapsed/Refractory Non-Hodgkin Lymphoma: Responses Observed in Diffuse Large B-Cell (DLBCL) and Follicular Lymphoma (FL) at Higher Cohort Doses

Bcl-2 protein expression is often increased as part of NHL pathogenesis. In approximately 90% of follicular lymphoma cases, Bcl-2 protein expression is dysregulated owing to the t(14;18) chromosome translocation.¹ By allowing tumor cells to evade apoptosis, Bcl-2 overexpression contributes to chemotherapy resistance. Therefore, mitigation of Bcl-2 activity presents an attractive goal for therapeutic development. Earlier drugs, such as navitoclax,

inhibited both Bcl-2 and Bcl-xL, leading to thrombocytopenia. ABT-199 is a potent, orally available molecule that selectively inhibits Bcl-2 (Figure 9).

To investigate the potential of this second-generation Bcl-2 inhibitor, a multicenter, international, dose-escalation, phase 1 study evaluated the safety and efficacy of ABT-199 in patients with relapsed or refractory NHL.² The primary objectives were to evaluate the safety and pharmacokinetics of ABT-

199, and to determine its maximum tolerated dose and recommended dose for the phase 2 trial. Secondary objectives were to assess the preliminary efficacy of ABT-199 and to explore potential biomarkers and pharmacogenetics. Eligible patients had histologically confirmed NHL that relapsed after therapy or was refractory. Patients had good performance status and adequate bone marrow, renal, and hepatic function. Patients who had undergone prior allogeneic

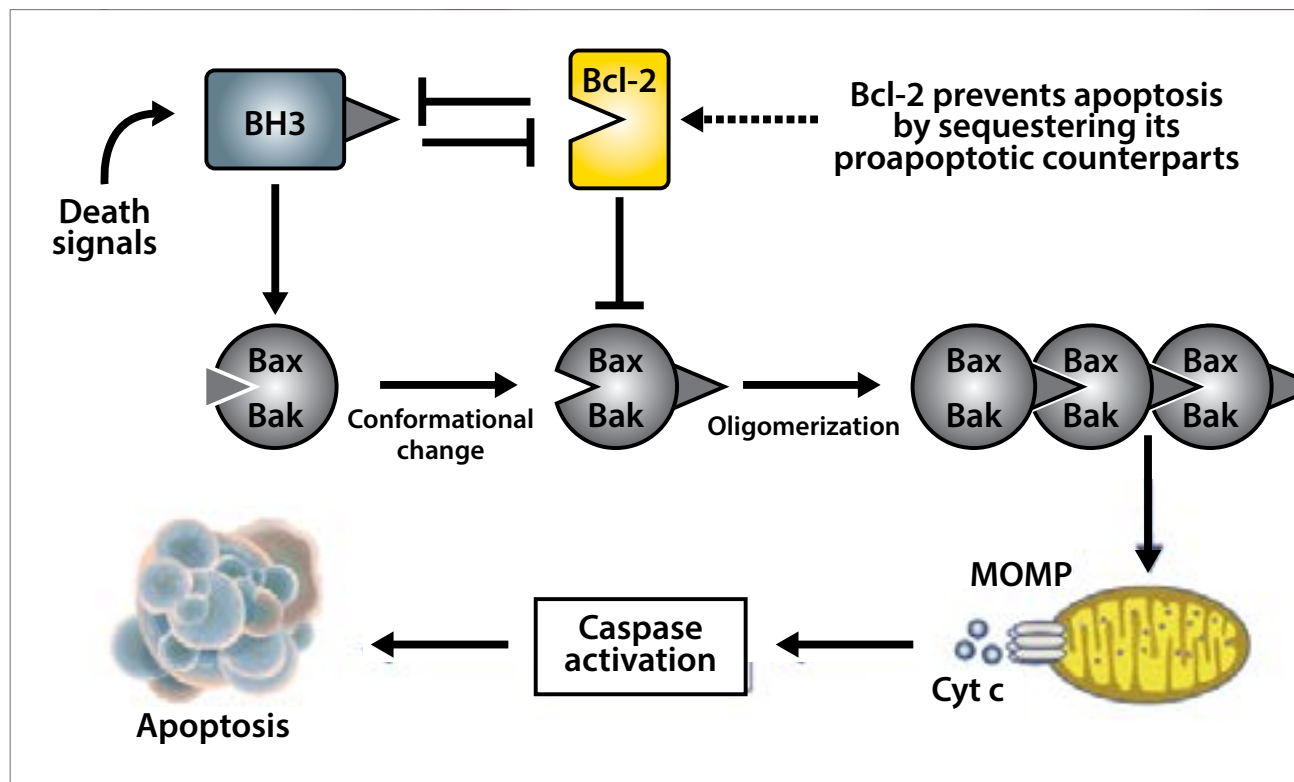


Figure 9. ABT-199 is a potent, orally available molecule that selectively inhibits Bcl-2.

SCT were excluded; however, patients who had relapsed after autologous SCT were allowed. Patients with Burkitt lymphoma, acute lymphocytic leukemia, or post-transplant lymphoproliferative disorder were excluded, as were those with active infection. The initial doses ranged from 50 mg to 400 mg and were escalated through a modified Fibonacci design. A single initial dose was administered 7 days prior to the study start for pharmacokinetic analysis. Based on these initial findings, an amended dose escalation scheme was devised, with separate regimens for MCL vs non-MCL NHL patients. For non-MCL NHL patients, dosing started at 400 mg during week 1. Daily dosing was then increased to 800 mg daily during week 2, with the maximum dose of 1200 mg reached during week 3. Some laboratory changes consistent with tumor lysis syndrome were observed in the MCL cohort, despite the absence of clinical manifestations. Therefore, a conservative dosing scheme was used for MCL patients. Dosing started at 20 mg daily, with escalation to 50 mg, 100 mg, 200 mg, and, ultimately, a designated cohort dose.

The 62 patients enrolled at the time of the presentation had a median age of 65 years, and a slight majority were male. The most common disease histologies included MCL (32%), DLBCL (31%), follicular lymphoma (23%), and Waldenström macroglobulinemia (7%). Several patients had Richter's transformation. Nearly half of patients had bulky lymphadenopathy at study entry, with lymph node conglomerates of at least 5 cm. Patients had received a median of 3 prior therapies, and more than one-fourth had received 5 or more prior therapies. Ten patients had relapsed after autologous SCT. The median time on study was approximately 4 months, with many of the cohorts continuing to accrue patients at the time of the analysis.

The time in the study was approximately 5 months for MCL patients, 7 months for follicular lymphoma patients, and 19 months for Waldenström macroglobulinemia patients. Among the 63%

of patients who discontinued treatment, most did so owing to progressive disease. However, 3 patients were able to continue to allogeneic SCT with ongoing response. One patient discontinued owing to an AE manifesting as arthritis, and 1 patient died from disease progression. Two patients withdrew consent. There were 2 dose-limiting toxicities at the target dose of 600 mg: grade 3 febrile neutropenia and grade 4 neutropenia. Both of the patients who experienced these toxicities received treatment with growth factor support and remained enrolled in the study. After a single dose taken with a high-fat meal (which increases the area under the curve by 3-fold to 4-fold), the maximum plasma concentration is achieved in approximately 8 hours, with a half-life of approximately 15 hours that allows for daily dosing.

The 59 evaluable patients yielded an ORR of 48%, including 5% CRs. The MCL patients exhibited an ORR of 68%, including 1 CR. Responses were also observed in patients with DLBCL and follicular lymphoma, with all of the follicular lymphoma responses occurring at doses of 600 mg or greater. One 66-year-old patient with MCL diagnosed

in 2007 had exhibited transient responses to multiple lines of chemotherapy and radiation. After a course of radiation in 2012, she experienced disease progression and entered the study in 2013 with a baseline mass measuring 7.6 cm by 3.6 cm. By week 6 of the study, the patient exhibited a complete clinical resolution of the lymph node and remained in CR 8 months after initiating treatment. Another patient with DLBCL had relapsed after autologous SCT. She experienced a complete CR after treatment with ABT-199, subsequently underwent an allogeneic SCT, and remained in CR 1 year after transplant. The study is ongoing for the higher doses, including a cohort at 1200 mg for MCL patients and 2 safety expansion cohorts for patients with follicular lymphoma and DLBCL.

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ABSTRACT SUMMARY PET-Adapted Treatment Modification in Early Stage Hodgkin Lymphoma: a Systematic Review and Meta-Analysis

Hodgkin lymphoma is one of the most common malignancies in young adults and has cure rates as high as 90%. Hodgkin lymphoma treatment varies with the stage of diagnosis but is typically treated with chemotherapy and radiotherapy. Fluorodeoxyglucose (FDG)-PET scans are often used to determine the subsequent amounts of radiotherapy administered to the patient. To assess the consequences of adapting radiotherapy treatment based on FDG-PET assessments, a systematic review of the literature was performed (Abstract P1045). The review included all randomized controlled trials comparing FDG-PET-adapted therapy to standard treatment in previously untreated patients with early-stage Hodgkin lymphoma. Search results were screened, and relevant study data were identified by 2 independent authors. Data extraction was conducted according to the guidelines proposed by the Cochrane Collaboration. The meta-analysis included 3 randomized controlled trials involving a combined 1480 participants. At a median follow-up of 34 months, the median PFS was inferior for patients who did not receive radiotherapy based on FDG-PET results compared with the standard treatment arm (HR, 2.16; 95% CI, 1.36-3.42; $P=$.001). AEs were reported only in 1 study, and no significant differences were observed between the 2 arms.

Safety and Efficacy of Brentuximab Vedotin (SGN-35) in Hodgkin Lymphoma Patients Undergoing Reduced Intensity Allogeneic Stem Cell Transplant Following a Relapse After Autologous Transplant

Despite improvements in response rates and long-term PFS for Hodgkin lymphoma patients, approximately 1 in 7 patients with early-stage disease and as many as 40% of patients with advanced-stage disease either fail to achieve CR or relapse within a few years of the initial treatment.¹ Moreover, patients who undergo subsequent high-dose chemotherapy followed by autologous SCT show a long-term disease-free survival rate of approximately 50% to 60%. Among those who then relapse, there are candidates for allogeneic SCT, which can induce some durable remissions. However, the applicability of allogeneic SCT is limited by the challenge in obtaining an objective response prior to the allogeneic transplant. Brentuximab vedotin has shown efficacy in achieving disease control in patients who relapse after autologous SCT, demonstrating a 2-year PFS of 66% and an estimated 2-year survival rate of 80% in a case series of 15 patients.²

A retrospective analysis evaluated the efficacy and safety of brentuximab vedotin monotherapy as a bridge to allogeneic transplant in 10 Hodgkin lymphoma patients who relapsed after autologous SCT.³ The analysis included 10 patients who had received brentuximab vedotin in this setting at

4 hematologic divisions in Northern Italy between August 2011 and September 2013. Patients had a median age of 32 years (range, 21-61 years) and had received a median of 5 prior regimens. Patients received a median of 6 cycles (range, 4-7) of brentuximab vedotin, and the median time from the last dose of brentuximab vedotin to the allogeneic SCT was 1 month (range, 1-5 months). All patients received a reduced-intensity conditioning regimen. Although 1 patient had a human leukocyte antigen-identical sibling, the remaining patients required either a matched unrelated donor or a haplo-identical donor. In the haplo-identical setting, graft-vs-host disease prophylaxis consisted of post-transplant cyclophosphamide plus tacrolimus with mycophenolate mofetil. Methotrexate and cyclosporine were administered to the remaining patients. Patients were monitored for engraftment, acute graft-vs-host disease, chimerism, and infectious complications per institutional standards.

There was 1 primary graft failure with autologous reconstitution, which was attributed to an underestimation of the optimal drug dose owing to the patient's high body mass index. All other patients achieved successful engraftment, with a median time to

neutrophil recovery of 20 days (range, 15-26 days). There was no delay of engraftment, no increased incidence of cytomegalovirus reactivations or other types of infections, and no cases of worsening neuropathy or grade 3/4 extrahematologic toxicities. Nonrelapse mortality at 1 year was 10%, and 1 patient experienced a relapse at 8 months after the allogeneic SCT. At a median follow-up of 12 months, the remaining patients were alive and progression-free. The authors concluded that brentuximab vedotin monotherapy can be safely and effectively administered prior to reduced-intensity conditioning followed by allogeneic SCT in Hodgkin lymphoma patients who have relapsed after autologous SCT.

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Highlights in Lymphoma From the 2014 European Hematology Association Congress

Craig H. Moskowitz, MD
 Clinical Director, Division of Hematologic Oncology
 Attending Physician, Lymphoma and Adult BMT Services
 Member, Memorial Sloan Kettering Cancer Center
 Professor of Medicine, Weill Medical College of Cornell University
 New York, New York

The 2014 European Hematology Association Congress was held in Milan, Italy. There were many important presentations on the management of lymphoma, some of which may eventually become practice-changing. Trials evaluated treatments such as brentuximab vedotin; doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD); bendamustine, gemcitabine, and vinorelbine; rituximab; and novel antibody-drug conjugates.

Brentuximab Vedotin

There were several interesting presentations on brentuximab vedotin. Two retrospective studies—one from France¹ and one from Italy²—examined the use of brentuximab vedotin in patients who have failed an autologous stem cell transplant (ASCT). The French study, which included 241 patients, was the largest study of brentuximab vedotin performed in the post-transplant lymphoma setting.¹ An interesting finding was that the best response was seen early in the course of treatment. After a median 4 cycles of treatment, the overall response rate was 61%, with 34% complete responses, in Hodgkin lymphoma patients. These data are similar to that of the pivotal trial.³ Once again, it is important to stress that those patients not achieving a complete response will progress within the next few months while receiving brentuximab vedotin, and treatment with a nonablative allogeneic stem cell

transplant should be considered in an expedited fashion. This approach is not needed in the one-third of patients who achieve a complete response, which can be durable.

A small retrospective study from Italy evaluated the use of brentuximab vedotin as a bridge to allogeneic transplant in 10 patients with Hodgkin lymphoma who relapsed after autologous stem cell transplant.² Patients received a median 6 cycles of brentuximab vedotin. A reduced-intensity conditioning regimen was used. All patients but 1 achieved successful engraftment. The median time to neutrophil recovery was 20 days. Nonrelapse mortality at 1 year was 10%.

A multicenter, retrospective study evaluated the use of brentuximab vedotin in 16 heavily pretreated patients with Hodgkin lymphoma who progressed following allogeneic stem cell transplant.⁴ An interesting finding is that, again, the best response was seen early at the first restaging, and those patients who achieved a complete response usually did so after a median of 4 cycles of chemotherapy. The overall response rate was 69%. Brentuximab vedotin was well-tolerated, with minimal side effects. It clearly offered the patients good palliation in this setting.

Brentuximab vedotin was combined with 2 variants of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) in patients with unfavorable advanced-stage Hodgkin lymphoma.⁵ It

was the largest study to examine brentuximab vedotin in combination with chemotherapy in the untreated Hodgkin lymphoma setting. Preliminary outcome data were presented for 48 patients, and safety data were available for 65. Both regimens were fairly well-tolerated, and brentuximab vedotin conferred no additive neurotoxicity. The planned enrollment of 100 patients is expected to be completed by the end of 2014. Based upon the results, subsequent random assignment trials will be initiated.

ABVD and Variants

Data were presented on an important analysis from the HD13 trial for early-stage favorable Hodgkin lymphoma by the German Hodgkin Disease Study Group.⁶ This large, random-assignment trial evaluated 4 regimens—ABVD; doxorubicin, vinblastine, and dacarbazine (AVD); doxorubicin, bleomycin, and vinblastine (ABV); and doxorubicin and vinblastine (AV)—each followed by involved field radiotherapy at 30 Gy. As was previously reported,⁷ the ABV arm and the AV arm were suboptimal, and the randomization continued with just ABVD or AVD. The primary endpoint was noninferiority in the AVD arm. Unfortunately, this endpoint was not achieved; there was a nearly 5% improvement in progression-free survival in patients who received ABVD vs AVD. The ABVD regimen remains the standard of care for early-stage Hodgkin lymphoma based on this study.

Bendamustine, Gemcitabine, and Vinorelbine

Unexpected results were seen in a study that evaluated the combination of bendamustine, gemcitabine, and vinorelbine as salvage therapy for patients with relapsed and refractory Hodgkin lymphoma.⁸ The primary goal of the study was to determine whether it is possible to effectively mobilize patients' peripheral blood stem cells. Previous data have suggested that bendamustine can adversely affect stem cell mobilization. In contrast, in the current study, 36 of 37 patients were able to achieve an adequate 3×10^6 CD34-positive cells/kg target yield, with a median of 8.6×10^6 CD34-positive cells/kg. The results of this study are favorable. Bendamustine, gemcitabine, and vinorelbine appeared to be a reasonable salvage approach for patients with relapsed and refractory disease eligible to undergo an ASCT.

Rituximab

In Europe, there is a strong impetus to administer rituximab subcutaneously, which takes minutes, as opposed to intravenously, which takes hours. The SABRINA (A Study of MabThera [Rituximab] Subcutaneous Vs. MabThera [Rituximab] Intravenous in Patients With Follicular Non-Hodgkin's Lymphoma) trial was a random-assignment trial in which more than 400 patients with non-Hodgkin lymphoma received rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) administered intravenously or rituximab administered subcutaneously with CHOP chemotherapy.⁹ All study endpoints were similar between the 2 treatment groups. The study concluded that CHOP chemotherapy plus rituximab administered subcutaneously over 5 minutes was equally efficacious to standard R-CHOP. This approach is expected to have a favorable impact on quality of life.

Antibody-Drug Conjugates

A phase 2 study evaluated 2 antibody-drug conjugates, polatuzumab vedotin and pinatuzumab vedotin, in combination with rituximab in relapsed and refractory diffuse large B-cell lymphoma and follicular lymphoma.¹⁰ Pinatuzumab vedotin binds to CD22 and polatuzumab vedotin binds to CD79b. Like brentuximab vedotin,³ these agents consist of an antibody conjugated with a cleavable peptide linker to the microtubule-disrupting agent monomethyl auristatin E. Data were presented on 63 patients who received pinatuzumab vedotin and 58 patients who received polatuzumab vedotin. In diffuse large B-cell lymphoma, the overall response rates were 57% with pinatuzumab and 56% with polatuzumab. Response rates were higher in follicular lymphoma, at 62% with pinatuzumab and 70% with polatuzumab. Both treatments were fairly well-tolerated. This study suggests that these agents should undergo further study in these settings.

ABT-199

ABT-199 is an oral small molecule that inhibits BCL2. Updated data were presented from a phase 1 trial of ABT-199 in patients with relapsed and refractory lymphoma.^{11,12} The analysis included 58 patients, who had a wide variety of non-Hodgkin lymphoma subtypes. The overall response rate was 48%. Among patients with mantle cell lymphoma, the overall response rate was 68%, with 1 complete response. It is important to note that there was a dose-response relationship; patients with diffuse large B-cell lymphoma and follicular lymphoma responded only when the doses were 600 mg or higher. Clearly, ABT-199 as a monotherapy has high anti-tumor activity. Several studies are exploring this agent as monotherapy and in combination with other agents.¹³⁻¹⁵

Acknowledgment

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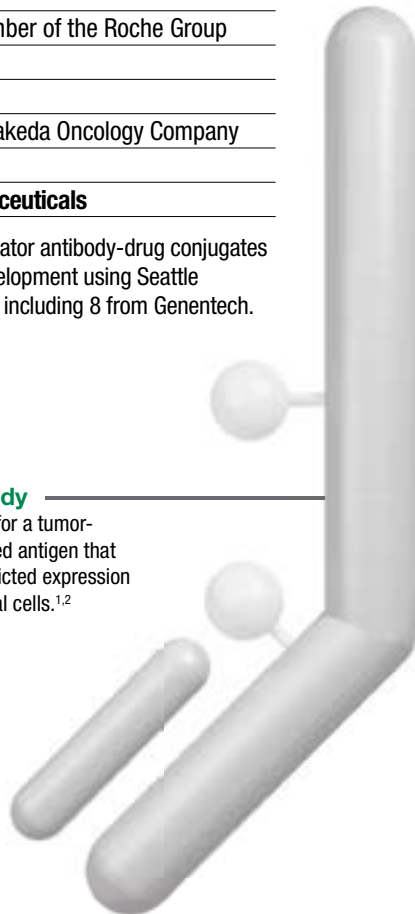
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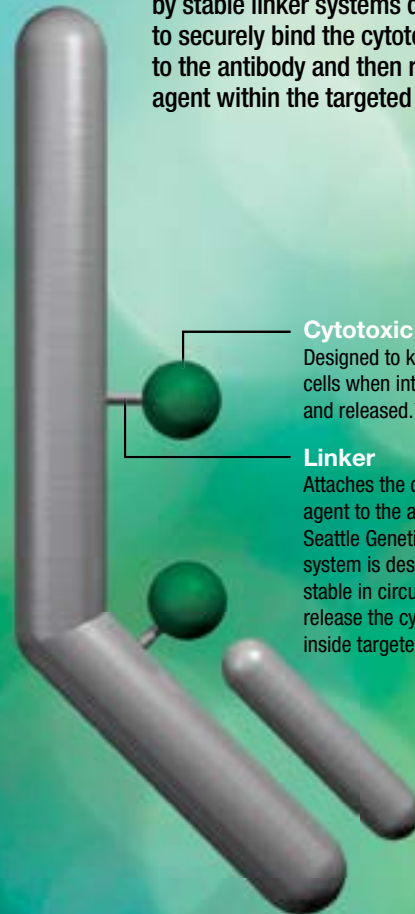
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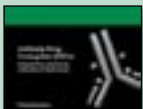
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