

A SPECIAL MEETING REVIEW EDITION

Highlights in Lymphoma From the 2013 American Society of Hematology Annual Meeting and Exposition

A Review of Selected Presentations From the 2013 American Society of Hematology Annual Meeting and Exposition • December 7-10, 2013
• New Orleans, Louisiana

Special Reporting on:

- A Phase 2 Study of Brentuximab Vedotin in Patients With Relapsed or Refractory CD30-Positive Non-Hodgkin Lymphomas: Interim Results in Patients With DLBCL and Other B-Cell Lymphomas
- A Phase I Study of Panobinostat in Combination With ICE (Ifosfamide, Carboplatin and Etoposide) in Patients With Relapsed or Refractory Classical Hodgkin Lymphoma (cHL)
- FDG-PET Adapted Sequential Therapy With Brentuximab Vedotin and Augmented ICE Followed by Autologous Stem Cell Transplant for Relapsed and Refractory Hodgkin Lymphoma
- Mature Response Data From a Phase 2 Study of PI3K-Delta Inhibitor Idelalisib in Patients With Double (Rituximab and Alkylating Agent)-Refractory Indolent B-Cell Non-Hodgkin Lymphoma (iNHL)
- Phase II Trial of Brentuximab Vedotin for CD30+ Cutaneous T-Cell Lymphomas and Lymphoproliferative Disorders
- Lenalidomide in Combination With R-CHOP (R2-CHOP) in Patients With High Burden Follicular Lymphoma: Phase 2 Study
- Reduced-Intensity Conditioning (RIC) and Allogeneic Stem Cell Transplantation (allo-SCT) for Relapsed/Refractory Hodgkin Lymphoma (HL) in the Brentuximab Vedotin Era: Favorable Overall and Progression-Free Survival (OS/PFS) With Low Transplant-Related Mortality (TRM)
- Combination Biologic Therapy Without Chemotherapy as Initial Treatment for Mantle Cell Lymphoma: Multi-Center Phase II Study of Lenalidomide Plus Rituximab

PLUS Meeting Abstract Summaries

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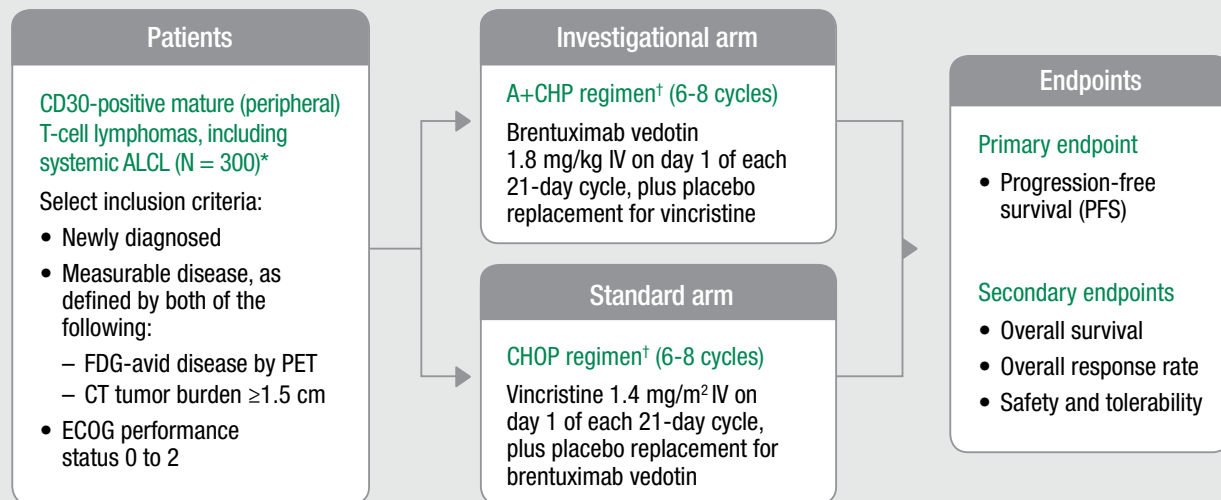


ECHELON-2

Assessing Brentuximab Vedotin and CHP in the Frontline Treatment of CD30-Positive Mature T-Cell Lymphomas

Assessing brentuximab vedotin in Frontline Peripheral T-cell Lymphomas

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*Eligible subtypes include anaplastic lymphoma kinase (ALK)-positive systemic anaplastic large cell lymphoma (ALCL) with an International Prognostic Index (IPI) score of ≥ 2 ; ALK-negative systemic ALCL; peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS); angioimmunoblastic T-cell lymphoma (AITL); adult T-cell leukemia/lymphoma (ATLL); enteropathy-associated T-cell lymphoma (EATL); and hepatosplenic T-cell lymphoma.

†Cyclophosphamide 750 mg/m² and doxorubicin 50 mg/m² will be administered IV on day 1; 100 mg oral prednisone will be administered on days 1-5 of each 21-day cycle.

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A Phase 2 Study of Brentuximab Vedotin in Patients With Relapsed or Refractory CD30-Positive Non-Hodgkin Lymphomas: Interim Results in Patients With DLBCL and Other B-Cell Lymphomas

Outcomes for patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) remain poor; autologous stem cell transplant (ASCT) yields limited efficacy in the rituximab era, and there is no standard of care for patients who are ineligible for transplant.¹ Brentuximab vedotin is an antibody-drug conjugate consisting of a CD30-directed monoclonal antibody linked with the microtubule-disrupting agent monomethyl auristatin E (MMAE). Brentuximab vedotin has demonstrated high response rates in patients with CD30-expressing B-cell malignancies, including Hodgkin lymphoma and systemic anaplastic large cell lymphoma.^{2,3} Recent studies indicate that between 14% and 25% of DLBCLs express CD30, including both activated B-cell type and germinal center subtypes, and CD30 expression is associated with a more favorable prognosis.^{4,5}

Based on these demonstrations of CD30 positivity, a phase 2 study was undertaken evaluating brentuximab vedotin in patients with CD30-positive relapsed or refractory non-Hodgkin lymphoma (NHL). Results were presented at the 2013 American Society of Hematology (ASH) meeting by Dr Nancy Bartlett.⁶ Patients were required to be at least 12 years old and to have an Eastern Cooperative Oncology Group (ECOG) score of 0 to 2 or a Lansky score of at least 50. Patients received intravenous brentuximab vedotin administered at 1.8 mg/kg every 3 weeks until disease progression or unacceptable toxicity.

The study enrolled 68 patients, of whom 50 (74%) had DLBCL. Of the DLBCL cases, 11 represented transformations from a prior indolent lymphoma or chronic lymphocytic

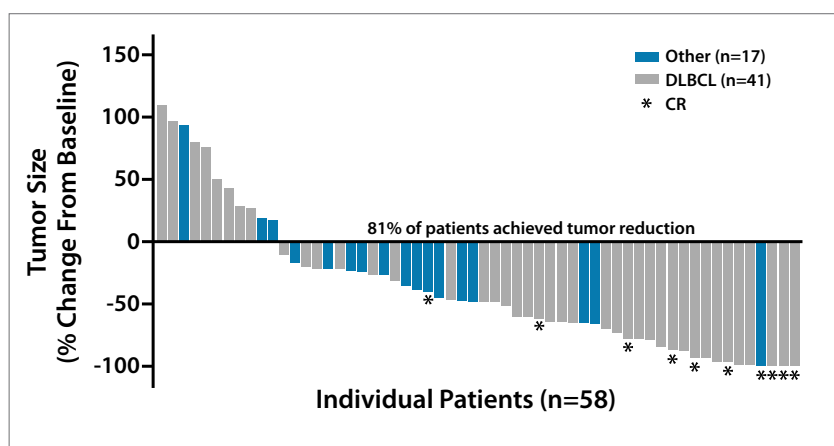


Figure 1. Interim results from a phase 2 study of brentuximab vedotin in patients with relapsed or refractory CD30-positive non-Hodgkin lymphomas showed that approximately 81% of patients had some degree of tumor reduction. CR, complete response; DLBCL, diffuse large B-cell lymphoma. Adapted from Bartlett NB et al. ASH abstract 848. *Blood*. 2013;122(21 suppl).⁶

leukemia. The median age was 63 years (range, 17-85 years) among patients with DLBCL and 36 years (range, 16-68 years) among the other patients. Patients had received a median of 2 to 3 prior systemic therapies, with 20% of patients receiving a prior ASCT. The majority of patients (74% of those with DLBCL and 89% of other patients) were refractory to frontline therapy, and 82% and 72% of patients, respectively, were refractory to the most recent prior therapy.

Patients were enrolled based on CD30 positivity as demonstrated by local laboratories; a second assessment of CD30 expression at a reference laboratory revealed significant variability in CD30 positivity (0% to 100%). The median percentage of CD30-positive malignant cells as determined by the central laboratory was 25% (range, 0%-100%) for DLBCL and 45% (range, 4%-80%) for other histologies. Levels of soluble CD30 were elevated in both DLBCL and non-DLBCL groups.

In the study, brentuximab vedotin was associated with an overall response rate (ORR) of 42% in patients with DLBCL, including 16% complete responses (CRs), and 22% in patients with other histologies, including 11% CRs. The median durations of response and CR were 5.8 months and 11.5 months, respectively, in the DLBCL group and 5.0 months and not reached in other patients. Median progression-free survival (PFS) was 4.0 months in the DLBCL group and 2.9 months in other patients. Patients received a median of 4 treatment cycles (range, 1-19). Approximately 81% of patients had some degree of tumor reduction (Figure 1). Patients received a median of 4 cycles of therapy.

Responses to brentuximab vedotin did not appear to vary based on CD30 expression (Table 1). Tumor reductions were observed across the spectrum of CD30 expression level; moreover, the percentage of patients with response or CR was similar among those with a

Table 1. Response According to CD30 Expression in Relapsed DLBCL

	CD30 Expression		
	0%-9% (n=14)	10%-100% (n=30)	Not Available (n=6)
Overall Response Rate	57%	40%	17%
Complete Response	29%	13%	-
Partial Response	29%	27%	17%
Stable Disease	7%	20%	50%
Progressive Disease	36%	37%	33%

DLBCL, diffuse large B-cell lymphoma. Adapted from Bartlett NB et al. ASH abstract 848. *Blood*. 2013;122(21 suppl).⁶

CD30 expression level of less than 10% and those with higher CD30 expression. Computer-assisted immunohistochemistry was used to further investigate the lack of association between CD30 expression and responses to brentuximab vedotin. Such an analysis was conducted on a tumor sample from a patient in whom 1% of malignant cells tested CD30-positive, yet the patient had a CR to

brentuximab vedotin. The more sensitive computer-assisted immunohistochemistry technique indicated CD30 positivity in 34% of malignant cells. Thus, previously undetected CD30 expression on malignant cells and elevated soluble CD30 levels have both been proposed as explanations for responses observed to brentuximab vedotin in patients with undetectable CD30.

ABSTRACT SUMMARY Three-Year Survival Results From an Ongoing Phase 2 Study of Brentuximab Vedotin in Patients With Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma

Updated survival results were presented from a multicenter, open-label, phase 2 study of brentuximab vedotin in patients with relapsed or refractory systemic ALCL (Abstract 1809). The trial had enrolled 58 patients, with a median age of 52 years (range, 14-76 years); 62% were refractory to frontline therapy, and 22% had no response to any prior treatment. Patients had received a median of 2 prior regimens (range, 1-6), and 26% had received prior ASCT. Brentuximab vedotin was administered at 1.8 mg/kg every 3 weeks. As previously reported (Pro B et al. *J Clin Oncol*. 2012;30(18):2190-2196), brentuximab vedotin demonstrated substantial clinical activity in relapsed/refractory systemic ALCL, with an ORR of 86%, including 57% CRs. The median durations of response and CR were 12.6 months and 13.2 months, respectively. This updated analysis presented results after a median follow-up of 33.4 months from the first dose (Abstract 1809). Of the 34 patients who had attained a CR with brentuximab vedotin, 47% (n=16) remained in remission at the most recent analysis. Ten of these patients underwent stem cell transplantation after brentuximab vedotin, and 6 received no additional therapy. Patients had received a median of 7 cycles of brentuximab vedotin (range, 1-16). Brentuximab vedotin therapy was restarted in 8 patients and was administered for an extended period (>16 cycles) in 4 patients. Overall, 64% of enrolled patients were alive at the most recent follow-up, for an estimated 3-year overall survival rate of 63%. The median overall survival was not yet reached for the overall population or for the patients who obtained a CR, and it was 7.7 months among patients not obtaining a CR. Based on the demonstrated efficacy and safety of brentuximab vedotin, the ongoing randomized phase 3 ECHELON-2 (A Comparison of Brentuximab Vedotin and CHP With Standard-of-Care CHOP in the Treatment of Patients With CD30-Positive Mature T-Cell Lymphomas) trial is evaluating the efficacy and safety of brentuximab vedotin in combination with CHP for the initial treatment of CD30-positive peripheral T-cell lymphomas, including systemic ALCL (ClinicalTrials.gov Identifier: NCT01777152).

Safety outcomes were generally similar to those observed in other studies of brentuximab vedotin. However, approximately 35% of patients developed grade 3/4 neutropenia; this higher rate was attributed to differences in the patient populations between studies. Serious adverse events occurring in more than 1 patient included pneumonia (n=3), anemia (n=2), febrile neutropenia (n=2), neutropenia (n=2), and thrombocytopenia (n=2). Peripheral sensory neuropathy was reported in 24% of patients. The primary reason for treatment discontinuation was disease progression (63%); 10% discontinued owing to adverse events. Of the 5 deaths that occurred within 30 days of treatment with brentuximab vedotin, all were disease-related.

Ongoing trials include a cohort of patients with DLBCL with undetectable CD30 expression by standard immunohistochemistry, and a study of brentuximab vedotin plus rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in patients with high-risk DLBCL without consideration of CD30 expression level.

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A Phase I Study of Panobinostat in Combination With ICE (Ifosfamide, Carboplatin and Etoposide) in Patients With Relapsed or Refractory Classical Hodgkin Lymphoma (cHL)

A variety of approaches are being evaluated for the treatment of relapsed or refractory classical Hodgkin lymphoma. Currently, salvage chemotherapy followed by ASCT is a common approach, with CR as assessed by positron emission tomography (PET) scanning predicting the most favorable prognosis. A regimen used in the salvage setting is ifosfamide, carboplatin, and etoposide (ICE), which has demonstrated CR rates of 26% by computed tomography scan, and up to 61% by PET scan using an augmented dosing regimen.^{1,2} Thrombocytopenia has been a significant concern associated with the regimen.

New agents have been evaluated to increase the efficacy of salvage therapy for patients with relapsed or refractory Hodgkin lymphoma. One is the histone deacetylase inhibitor panobinostat; histone deacetylation has been proposed to induce cell death through a variety of proposed mechanisms, including promotion of cell cycle arrest and apoptosis through epigenetic modification of gene expression and induction of antitumor immune responses through alterations of cytokine and chemokine production and inhibition of angiogenesis.³

Panobinostat, which is administered orally, has demonstrated antitumor activity in patients with relapsed or refractory classical Hodgkin lymphoma. In a phase 2 study of 129 patients with relapsed or refractory Hodgkin lymphoma after ASCT who had received a median of 4 prior systemic regimens (range, 2-7), panobinostat at 40 mg administered 3 times per week was associated with an ORR of 27% (4% CR), a median response duration of 7 months, and a median PFS of 6 months.⁴ Myelosuppression (in particular, reversible thrombocytopenia) is the primary dose-limiting toxicity associated with panobinostat.⁵

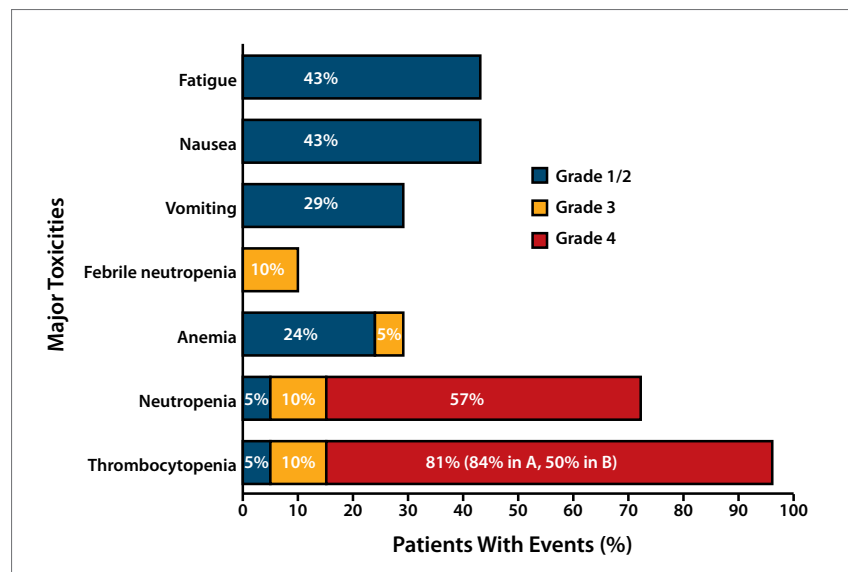


Figure 2. Major toxicities in a phase 1 study of panobinostat in combination with ICE in patients with relapsed or refractory classical Hodgkin lymphoma. ICE, ifosfamide, carboplatin, and etoposide. Adapted from Oki Y et al. ASH abstract 252. *Blood*. 2013;122(21 suppl).⁶

ABSTRACT SUMMARY High Response Rates to Crizotinib in Advanced, Chemoresistant ALK+ Lymphoma Patients

Crizotinib is an orally administered small-molecule inhibitor of anaplastic lymphoma kinase (*ALK*) that has demonstrated short-term activity in case reports of patients with *ALK*-positive lymphoma (Gambacorti-Passerini C et al. *N Engl J Med*. 2011;364(8):775-776). Dr Sara Redaelli presented results of a study evaluating the efficacy and safety of single-agent crizotinib in patients with advanced, previously treated *ALK*-positive NHL (Abstract 368). The 11 enrolled patients included 9 patients with ALCL and 2 patients with DLBCL. Responses to crizotinib, including 9 CRs and 1 partial response, were observed in 10 of 11 patients (91%). Responses were maintained for longer than 6 months in 6 patients, and the 2-year PFS was 63.7%. All CRs were obtained in patients with ALCL, yielding a CR rate of 100% with crizotinib in that population. All toxicities were grade 1/2; adverse events reported in more than 1 patient included ocular flashes (n=10), peripheral edema (n=3), and neutropenia (n=2). After a follow-up of 40 months, 4 patients with a CR continued to receive crizotinib, 3 patients underwent an allogeneic bone marrow transplant, and 4 patients developed disease progression. Mutations in the *ALK* kinase domain were identified in patients with relapse. Additional studies are under way evaluating crizotinib in both relapsed and previously untreated *ALK*-positive lymphomas.

Based on the demonstrated activity of panobinostat and its relatively acceptable safety profile, a single-center phase 1 study was undertaken evaluat-

ing this agent in combination with ICE in patients with relapsed or refractory classical Hodgkin lymphoma after a frontline standard anthracycline-con-

ABSTRACT SUMMARY A Phase 2 Study of Single-Agent Brentuximab Vedotin for Front-Line Therapy of Hodgkin Lymphoma in Patients Age 60 Years and Above: Interim Results

Dr Christopher Yasenachak presented interim results of an open-label phase 2 study evaluating the efficacy and safety of brentuximab vedotin in older adults with previously untreated Hodgkin lymphoma (Abstract 4389). The study enrolled 19 patients ages 60 years and older, with a median age of 78 years (range, 64-92 years). Their ECOG status was 0 to 3. Moderate age-related renal insufficiency was present at baseline in 12 of 19 patients (63%). Patients received single-agent intravenous brentuximab vedotin at 1.8 mg/kg every 3 weeks for up to 16 cycles. Patients who achieved stable disease or better had the option to continue beyond cycle 16. In this interim analysis, single-agent brentuximab vedotin was associated with an ORR of 89%, including 63% CRs. Treatment-related adverse events reported in more than 2 patients included peripheral sensory neuropathy (n=9), alopecia (n=4), fatigue (n=4), pruritus (n=3), and rash (n=3). In general, toxicities were grade 1/2 in severity, with the exception of 1 case each of peripheral sensory neuropathy, rash, neutropenia, and orthostatic hypotension, which were all grade 3 in severity. Notably, 5 patients had preexisting peripheral sensory neuropathy, and symptoms worsened with brentuximab vedotin in 2 of 5 patients.

taining regimen.⁶ Patients were required to have measurable disease of at least 2.0 cm, normal organ function, and a performance status of 0 to 2. They were age 16 years or older.

Initially, panobinostat was administered 3 times per week starting 1 week prior to ICE, with an initial dose of 20 mg once a day that was escalated to 30 mg once a day, in combination with a standard ICE regimen. However, this dosing schedule resulted in the development of significant cytopenia, necessitating frequent panobinostat dose interruptions during week 2 of ICE, with a median of 4 of 6 doses missed and grade 4 thrombocytopenia developing in 84% of patients. Based on these findings, the protocol was modified to omit panobinostat during treatment week 2 of ICE.

At ASH 2013, Dr Yasuhiro Oki reported results from 21 evaluable patients with a median age of 31 years (range, 19-60 years); 67% were male. The disease was refractory to initial therapy in 43% of patients. A single case of febrile neutropenia was the only dose-limiting toxicity observed in the dose-escalation cohort. Despite the development of grade 4 thrombocytopenia, no dose-limiting toxicities were observed in the 30-mg cohort, and thus this cohort was expanded for additional study.

The major toxicity observed across cohorts was the previously mentioned thrombocytopenia, reported in 84% of initially treated patients (Figure 2). At the time of the report, only 2 patients enrolled in the modified dosing schedule cohort had been evaluated for safety,

although accrual continues. Grade 4 neutropenia was reported in 57% of patients overall, and 10% of patients developed febrile neutropenia. No treatment-related deaths were reported.

Panobinostat plus ICE was associated with an ORR of 86%, including 71% CR. Of the 18 patients with a response to therapy, 17 proceeded directly to ASCT, and the remaining patient refused ASCT. An additional 3 patients received at least 1 additional therapy and then proceeded to ASCT. Stem cell harvesting and engraftment were successful in all 20 patients who underwent ASCT.

The investigators noted that the modified regimen, in which panobinostat is omitted during week 2 of ICE, continues to be evaluated, with the trial currently accruing patients.

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FDG-PET Adapted Sequential Therapy With Brentuximab Vedotin and Augmented ICE Followed by Autologous Stem Cell Transplant for Relapsed and Refractory Hodgkin Lymphoma

Patients with relapsed/refractory Hodgkin lymphoma who achieve a CR—as assessed by PET—at the time of ASCT have a significantly better prognosis than patients who do not achieve a CR according to PET. Five-year PFS rates were 79% and 23%, respectively ($P < .001$), and 5-year overall survival rates were 90% and 55%, respectively ($P = .001$).¹ Given the demonstrated efficacy of brentuximab vedotin in patients with relapsed/refractory Hodgkin lymphoma after ASCT,² a phase 2 study was undertaken evaluating the feasibility of administering single-agent brentuximab vedotin prior to ASCT in patients with relapsed/refractory Hodgkin lymphoma, using sequential ICE for patients not attaining PET normalization (Deauville ≥ 2) with brentuximab vedotin alone.³

The study enrolled 42 patients with Hodgkin lymphoma previously treated with 1 prior regimen. The median age was 31 years (range, 13-65 years), and 59% were male. Half of patients had primary refractory disease, and 33% of relapses had occurred within a year of the initial diagnosis. Patients received brentuximab vedotin weekly at 1.2 mg/kg intravenously on a 3-weeks-on, 1-week-off schedule for 2 cycles, followed by PET staging. Twelve patients (29%) attained PET normalization after brentuximab vedotin alone; 11 of these patients proceeded to high-dose chemotherapy and ASCT.

Thirty patients (71%) did not attain PET normalization with brentuximab vedotin and went on to receive 2

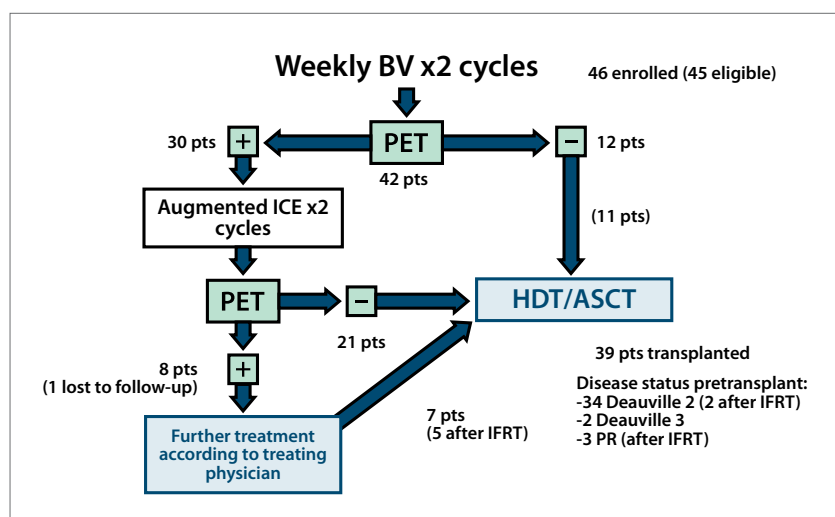


Figure 3. Treatment in a phase 2 trial evaluating the feasibility of administering single-agent brentuximab vedotin prior to ASCT in patients with relapsed/refractory Hodgkin lymphoma, using sequential ICE for patients not attaining PET normalization with brentuximab vedotin alone. ASCT, autologous stem cell transplant; BV, brentuximab vedotin; HDT, high-dose therapy; ICE, ifosfamide, carboplatin, and etoposide; IFRT, involved field radiation therapy; PET, positron-emission tomography; pts, patients. Adapted from Moskowitz A et al. ASH abstract 2099. *Blood*. 2013;122(21 suppl).³

cycles of augmented ICE (Figure 3). In this group, 21 patients (70%) attained PET normalization and proceeded to ASCT, 8 patients received further treatment, and 1 patient was lost to follow-up. The most common serious adverse event related to augmented ICE was febrile neutropenia, reported in 18 patients (43%).

Overall, 93% of evaluable patients underwent ASCT. After a median follow-up of 10 months posttransplant, 92% of patients remained progression-free. Of the remaining patients, 2 relapsed, subsequently received additional therapy, and proceeded to allogeneic stem cell transplantation; 1

patient relapsed and enrolled on a brentuximab vedotin combination study; and 1 patient died owing to progressive multifocal leukoencephalopathy.

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Mature Response Data From a Phase 2 Study of PI3K-Delta Inhibitor Idelalisib in Patients With Double (Rituximab and Alkylating Agent)-Refractory Indolent B-Cell Non-Hodgkin Lymphoma (iNHL)

More effective therapies are needed for patients with refractory indolent NHL, as currently there are few effective options for these patients. Idelalisib is a selective oral inhibitor of phosphatidylinositol 3-kinase (PI3K)-delta, a protein that has been implicated in multiple signaling pathways important to the survival and function of malignant B cells, including B-cell receptor signaling, proliferation, chemokine secretion, motility, homing, and adhesion. Treatment of malignant B cells with idelalisib inhibits proliferation and induces apoptosis, inhibits homing and retention of malignant B cells in lymphoid tissues, and reduces survival. In a phase 1 study, idelalisib demonstrated activity inducing durable responses in patients with heavily pretreated indolent non-Hodgkin lymphoma.¹

Based on the preclinical rationale and phase 1 findings, a phase 2 study was undertaken evaluating idelalisib monotherapy in patients with previously treated indolent NHL refractory to both rituximab and an alkylating agent.² Refractoriness to these therapies was documented radiographically and was defined as attaining less than a partial response on therapy or disease progression within 6 months of completing therapy. Patients were required to have measurable disease (≥ 2 cm), adequate performance status (ECOG 0-2 or Karnofsky ≥ 60), and adequate organ function. Patients received idelalisib 150 mg twice daily, with treatment continuing until progression. The study enrolled 125 patients (64% male), with a median age of 64 years (range, 33-87 years). The most common NHL

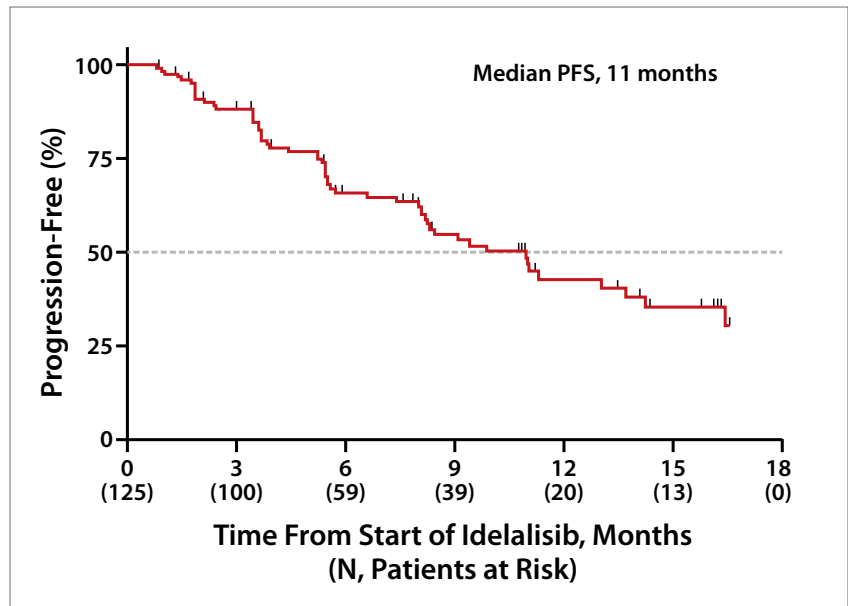


Figure 4. PFS in a phase 2 study of idelalisib in patients with refractory, indolent B-cell non-Hodgkin lymphoma. PFS, progression-free survival. Adapted from Gopal A et al. ASH abstract 85. *Blood*. 2013;122(21 suppl).²

subtype was follicular lymphoma (58%), followed by small lymphocytic lymphoma (22%), marginal zone lymphoma (12%), and lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia (8%). Lactate dehydrogenase was elevated in 30% of patients, and nearly half of patients (47%) had bulky disease, defined as 5 cm or greater. Patients had received a median of 4 prior regimens (range, 2-12). Other prior therapies in addition to rituximab and an alkylating agent included bendamustine (65%), an anthracycline (64%), a purine analogue (33%), and stem cell transplantation (11%). In 79% of patients, the disease was refractory to at least 2 prior regimens.

Overall, idelalisib was associated with an ORR of 57%, including 6% CRs. Responses occurred fairly rapidly,

with a median time to response of 1.9 months. The median duration of response was 12.5 months, and the median PFS was 11 months (Figure 4). Improvements in lymphadenopathy were observed in 90% of patients, with 57% of patients attaining improvements of at least 50% from baseline (Figure 5). Responses to idelalisib were observed independent of the number of prior therapies, response to prior therapies, and histologic subtypes.

The median duration of idelalisib treatment was 6.6 months (range, 0.6-23.9 months). At the time of the last analysis, 68% of patients had discontinued treatment, most commonly owing to disease progression (32%) or an adverse event (20%). Overall, idelalisib was associated with a manageable safety profile. The most common grade

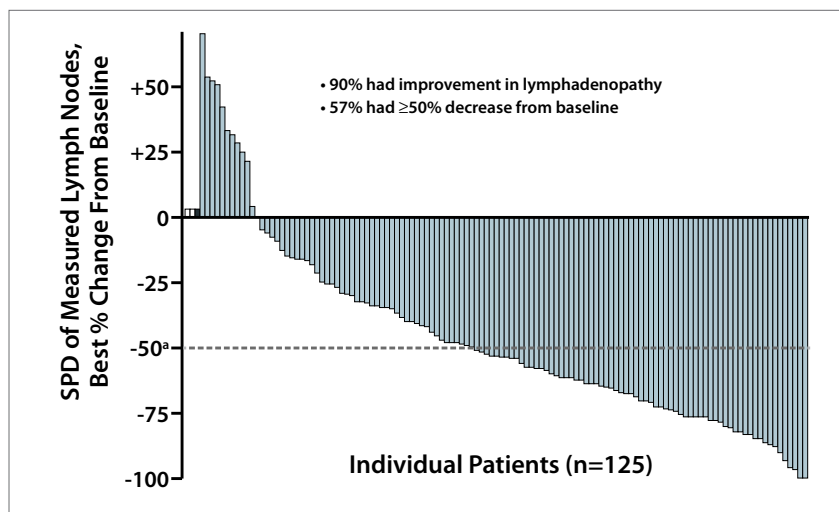


Figure 5. Lymph node response in a phase 2 study of idelalisib in patients with refractory, indolent B-cell non-Hodgkin lymphoma. SPD, sum of the products of the greatest perpendicular diameters. Adapted from Gopal A et al. ASH abstract 85. *Blood*. 2013;122(21 suppl).²

ABSTRACT SUMMARY Combining Ibrutinib With Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP): Updated Results From a Phase 1b Study In Treatment-Naïve Patients With CD20-Positive B-Cell Non-Hodgkin's Lymphoma (NHL)

A phase 1b study aimed to determine the recommended phase 2 dose (RP2D) of ibrutinib in combination with standard R-CHOP in treatment-naïve patients with CD20-positive B-cell NHL (Abstract 852). This open-label, nonrandomized, multicenter study consisted of 2 parts: dose escalation (Part 1) and dose expansion (Part 2). Ibrutinib was administered at dosages of 280 mg/d, 420 mg/d, or 560 mg/d combined with standard R-CHOP and prednisone. There were 2 dose-limiting toxicities in the 280 mg cohort (n=7), 1 transient syncope and 1 periorbital cellulitis; none in the 420 mg cohort (n=4), and 1 (grade 2 gastritis) in the 560 mg cohort (n=6). The recommended phase 2 dose was established as 560 mg ibrutinib. Across parts 1 and 2, the most common all-grade adverse events were neutropenia (67%), nausea (67%), thrombocytopenia (61%), vomiting (48%), anemia (36%), fatigue (30%), diarrhea (30%), headache (27%), constipation (27%), and alopecia (27%). Adverse events of grade 3 or higher were reported in 24 patients; the most common were neutropenia (61%), thrombocytopenia (21%), and anemia (18%). Serious adverse events were reported in 15 patients. The ORR for all evaluable patients in parts 1 and 2 was 100%. Among the 15 patients in part 1, 73% achieved a CR and 27% achieved a partial response. Final data for part 2 and DLBCL patients was not available at the time of this report. An interim analysis of 15 patients in part 2 showed that 60% achieved a CR and 40% achieved a partial response. Interim analysis for DLBCL patients showed a CR of 64% and a PR of 36%. R-CHOP did not affect the pharmacokinetics of ibrutinib, and ibrutinib did not alter the pharmacokinetics of vincristine.

3 or higher adverse events were diarrhea (13%) and pneumonia (7%); 10.4% of patients developed pyrexia. The proportion of patients with grade 3 or higher neutropenia increased from 5% at baseline to 27% during the study. Transaminase elevations developed in 48% and were grade 3 or higher in 12%. Grade 1/2 elevations resolved with continued idelalisib treatment, whereas elevations of grade 3 or higher were reversible with drug interruptions and did not recur upon restarting idelalisib in the majority of cases.

Based on these findings, the investigators concluded that idelalisib appears to confer high response rates and meaningful disease control in patients with indolent NHL refractory to both rituximab and alkylating agents.

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Phase II Trial of Brentuximab Vedotin for CD30+ Cutaneous T-Cell Lymphomas and Lymphoproliferative Disorders

Brentuximab vedotin is currently approved by the US Food and Drug Administration for use in patients with systemic anaplastic large cell lymphoma (ALCL) and relapsed/refractory Hodgkin lymphoma, both of which are characterized by CD30 expression. Some types of cutaneous lymphoproliferative disorders also express CD30, including primary cutaneous ALCL of the skin, lymphomatoid papulosis, and some cases of transformed mycosis fungoides, suggesting a rationale for the use of brentuximab vedotin in these patients. A single-center phase 2 trial was therefore undertaken evaluating brentuximab vedotin in patients with CD30-positive cutaneous T-cell lymphomas and lymphoproliferative disorders.¹

Patients were required to have had skin lesions with demonstrated CD30 positivity in the last 3 years; other eligibility requirements varied based on the type of disorder. Patients with lymphomatoid papulosis were required to have at least 10 lesions per month requiring systemic therapy, patients with primary cutaneous ALCL had to have refractory tumors (regional lymph node involvement was allowed), and patients with mycosis fungoides were required to have at least stage IB disease that had been treated with 1 or more prior systemic or topical therapies (transformed mycosis fungoides was allowed) and an ECOG performance status of 0 to 2. Biopsies were obtained from each type of clinical lesion at baseline, and CD30 expression was confirmed by a single dermatopathologist. Patients received brentuximab vedotin administered at 1.8 mg/kg over 30 minutes every 21 days for 8 cycles, or up to 16 doses for patients with a partial response. Patients attaining a CR discontinued therapy after 2 additional doses.

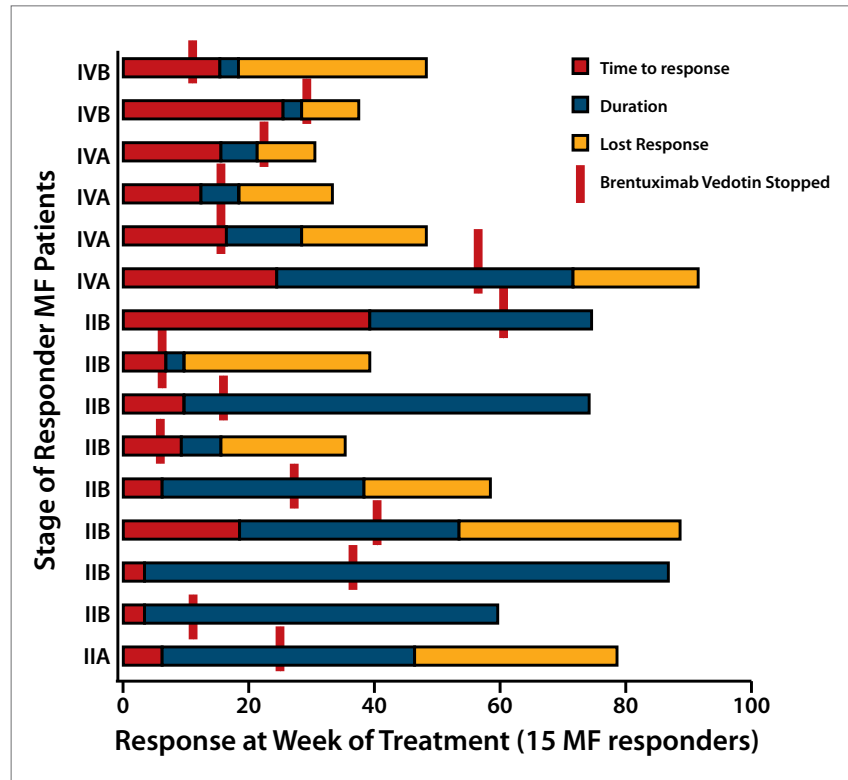


Figure 6. Time to response and duration of response among patients with MF in a phase 2 trial of brentuximab vedotin. MF, mycosis fungoides. Adapted from Duvic M et al. ASH abstract 367. *Blood*. 2013;122(21 suppl).¹

Of the 56 patients who enrolled and provided consent, 48 patients had received at least 2 doses of brentuximab vedotin and were included in the analysis. The median age of evaluable patients was 59.5 years; 54% were male and 63% were white. The disease distribution of enrolled patients consisted of mycosis fungoides (n=28), lymphomatoid papulosis (n=9), cutaneous ALCL (n=2), and mixed lesions (n=9). Dose reductions to 1.2 mg/kg were required in 12 patients owing to grade 2 peripheral neuropathy (n=9), liver function (n=2), and arthralgias (n=2).

Brentuximab vedotin was associated with an ORR of 73% across all disease types; the response rate among

patients with mycosis fungoides, determined by a 50% reduction in modified Severity Weighted Assessment Tool, was 54% (15 of 28), including 2 CRs. Among patients with ALCL, the response rate as assessed by the tumor measurements of index lesions was 2 of 2 (100%), both CRs. All 9 patients with lymphomatoid papulosis achieved a response, as defined by a 50% decrease in active lesion count. There were 5 CRs in this group. Of the 9 patients with mixed lesions, all achieved a response, including 8 patients with CRs.

The median time to response was 12 weeks (range, 3-39 weeks) in patients with mycosis fungoides and 3 weeks

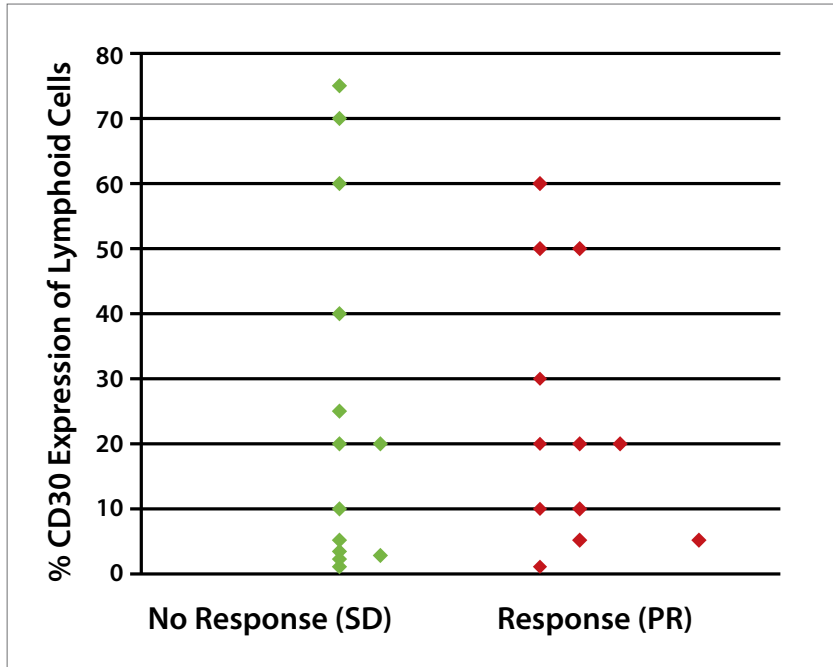


Figure 7. In a phase 2 trial of brentuximab vedotin, responses were observed across the spectrum of CD30 expression in patients with mycosis fungoides (n=28). PR, partial response; SD, stable disease. Adapted from Duvic M et al. ASH abstract 367. *Blood*. 2013;122(21 suppl).¹

ABSTRACT SUMMARY A Randomized Phase II Study Comparing Consolidation With a Single Dose of 90y Ibritumomab Tiuxetan (Zevalin®) (Z) Vs. Maintenance With Rituximab (R) for Two Years in Patients With Newly Diagnosed Follicular Lymphoma (FL) Responding to R-CHOP. Preliminary Results At 36 Months From Randomization

Dr Arnando López-Guillermo presented results of a randomized phase 2 study comparing consolidation with ibritumomab tiuxetan vs maintenance with rituximab plus R-CHOP in patients with follicular lymphoma (Abstract 369). Two years of rituximab maintenance therapy was associated with a longer PFS than consolidation therapy with a single dose of 90Y ibritumomab tiuxetan. No significant differences were seen in time to next treatment and overall survival. The study enrolled 126 patients with grade 1, 2, or 3a CD20-positive follicular lymphoma. All patients had attained a response to R-CHOP, and they had adequate blood counts. They were randomly assigned to consolidation therapy with a single dose of 90Y ibritumomab tiuxetan administered at 0.4 mCi/kg (total dose limit of 32 mCi) plus rituximab at 250 mg/m² at days -8 and 0 (n=64) or maintenance therapy with rituximab administered at 375 mg/m² every 8 weeks for 12 doses (24 months; n=62). Maintenance rituximab was found to be more effective than 90Y ibritumomab tiuxetan as assessed by the proportion of patients who were progression-free at 3 years in the overall population (77% vs 63%; HR, 0.517 [95% CI, 0.269-0.996; P=.044]). However, this difference was observed only among patients with a partial response to R-CHOP; among patients with a CR to R-CHOP, there was no significant difference in PFS between the arms. Both treatments were reasonably well tolerated, and no unexpected toxicities were noted.

(range, 3-9 weeks) among patients with ALCL, lymphomatoid papulosis, and mixed lesions. Some patients developed disease flares that were manageable, and, in some cases, hypersensitivity reactions were followed by responses to treatment.

The median duration of response was 32 weeks (range, 3-93 weeks) in patients with mycosis fungoides (Figure 6) and 26 weeks (range, 6-44 weeks) in patients with ALCL, lymphomatoid papulosis, and mixed lesions. In most cases, discontinuation of brentuximab vedotin was associated with loss of response. In some patients, restarting brentuximab vedotin off-trial induced a second response. After 1.5 years, 50% of patients remained progression-free; the median overall survival had not been reached at the time of the last analysis.

Among the 28 patients with mycosis fungoides, responses to brentuximab vedotin were observed across the spectrum of CD30 expression (Figure 7). There was no correlation between baseline CD30 expression level and likelihood of response to brentuximab vedotin; responses were observed in patients with low CD30 expression and were not observed in every patient with high CD30 expression. In fact, baseline CD30 levels were lower in patients with a CR than in those with a partial response or stable disease.

Most adverse events were mild. The most common grade 3 adverse events were neutropenia and nausea. Six patients withdrew early owing to sepsis (n=1), urosepsis (n=1), infusion reaction (n=1), fatigue (n=1), stable angina (n=1), and withdrawal of consent (n=1). Peripheral neuropathy was reported in 65% of patients, after a median treatment duration of 6 weeks for grade 1 events and 12 weeks for grade 2 events. Neuropathy resolved in 45% of patients after a median of 41.5 weeks.

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Lenalidomide in Combination With R-CHOP (R2-CHOP) in Patients With High Burden Follicular Lymphoma: Phase 2 Study

It is well established that in patients with follicular lymphoma, deeper responses to frontline therapy are associated with improved overall survival.^{1,2} Moreover, for patients with follicular lymphoma and a high tumor burden, the combination of R-CHOP has demonstrated longer PFS compared with other combination regimens.³ The addition of other agents to R-CHOP may further increase the depth of response, leading to improved outcomes in patients with high-burden follicular lymphoma.

One such agent under evaluation is lenalidomide, an immunomodulatory drug that demonstrated single-agent activity in relapsed indolent lymphoma and appears to augment the activity

of rituximab in preclinical models.^{4,5} The combination of lenalidomide and rituximab has demonstrated antitumor activity in both relapsed and previously untreated follicular lymphoma.⁶⁻⁸ Given the demonstrated efficacy of lenalidomide as a single agent and in combination with rituximab, the addition of lenalidomide to R-CHOP has been proposed to further enhance the efficacy of initial therapy for follicular lymphoma. This regimen, known as R2-CHOP, has been evaluated in several phase 1 studies in patients with B-cell lymphomas, demonstrating safety in both aggressive and indolent lymphomas.⁹⁻¹¹

A multicenter, open-label, phase 2 study was undertaken to evaluate the efficacy and safety of R2-CHOP

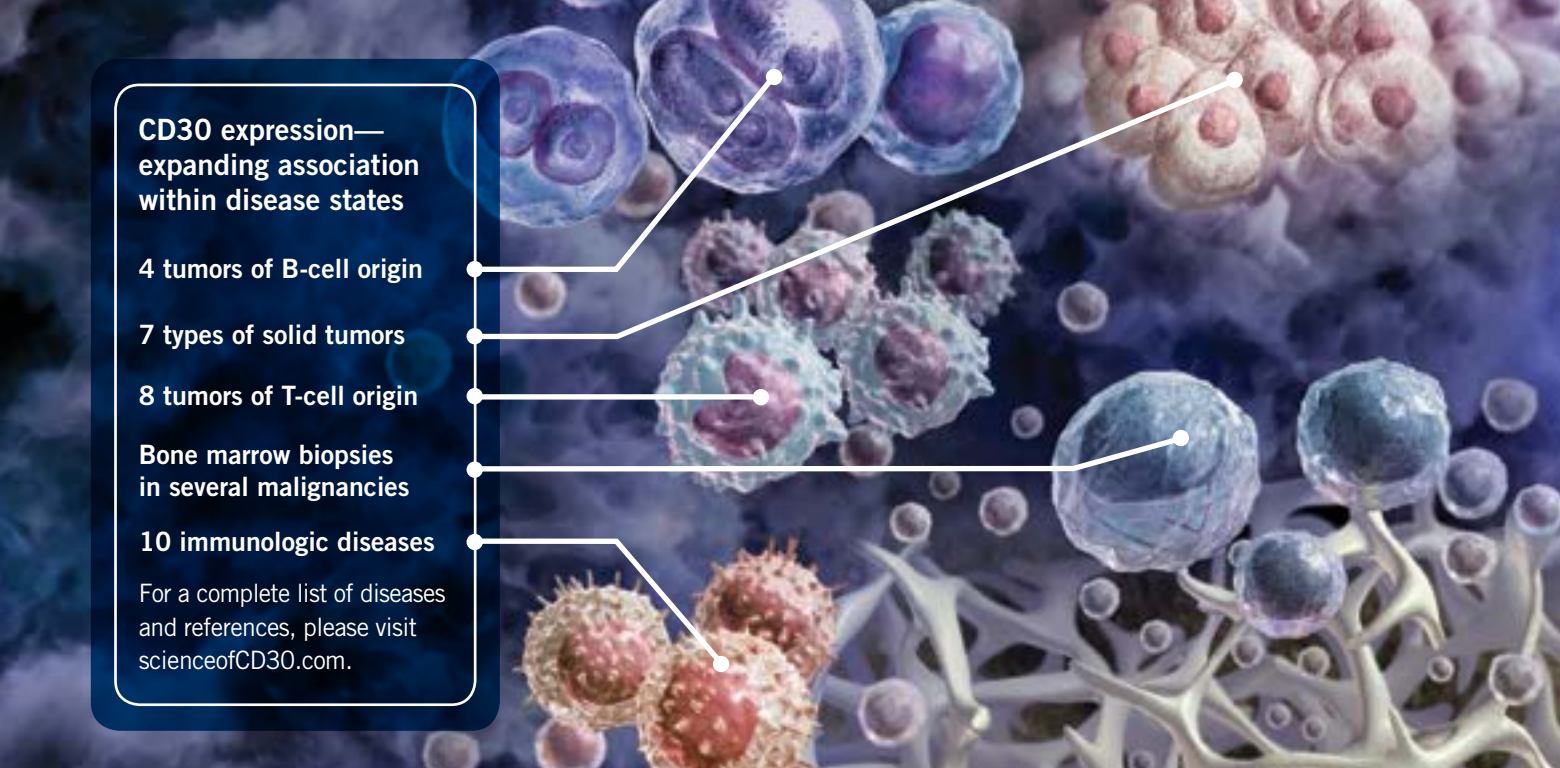
in patients with previously untreated high-burden follicular lymphoma.¹² The trial enrolled 80 follicular lymphoma patients with a World Health Organization grade of 1, 2, or 3a and bulky disease according to the Groupe d'Etude des Lymphomes Folliculaires criteria. No prior immunotherapy or chemotherapy was allowed. Patients were required to have an ECOG performance status of 0 to 2; in 69%, the status was 0. The patient's median age was 57 years (range, 29-71 years), and 50% of patients were male. Overall, 63% of patients had a high Follicular Lymphoma International Prognostic Index (FLIPI); 93% had stage III or IV disease, 40% had elevated lactate dehydrogenase, and 53% had evidence of bone marrow involvement.

Patients received 6 cycles of standard R-CHOP in combination with lenalidomide administered at 25 mg daily on days 1 to 14 of each cycle, with the dose modified in the event of toxicity. Patients also received pegfilgrastim at each cycle, aspirin at 100 mg during the induction treatment, and pneumocystis prophylaxis. Following completion of induction therapy and 2 additional rituximab infusions, patients were assessed for response. Patients attaining a response to induction therapy subsequently received rituximab maintenance therapy administered every 2 months for 2 years.

Among the 80 evaluable patients, R2-CHOP was associated with an ORR of 94%, including 74% CRs. The investigators conducted historical comparison of these outcomes against those obtained with R-CHOP in groups of patients from the PRIMA (Primary Rituximab and Maintenance) and PET-FL trials matched for age, sex, and

ABSTRACT SUMMARY Brentuximab Vedotin Improves HCT-CI, CR Status, and Peri-Transplant Toxicity in Patients With Relapsed/Refractory Hodgkin Lymphoma Heading to RIC Allo-HCT

In patients with relapsed/refractory Hodgkin lymphoma, RIC allo-HCT sometimes induces durable remissions, but outcomes can be compromised owing to comorbidities, inadequate disease control prior to transplant, and treatment-related morbidity and mortality. Dr Robert Chen presented results of a retrospective analysis indicating that in patients with relapsed/refractory Hodgkin lymphoma preparing to undergo RIC allo-HCT, brentuximab vedotin was associated with multiple advantages over regimens that did not contain brentuximab vedotin, including a lower incidence of comorbidities, a higher CR rate, and a lower incidence of adverse events during and after the transplant period (Abstract 3374). In their analysis, the investigators compared prior regimens, comorbidities, and outcomes among 21 patients who had received brentuximab vedotin and 23 patients who had not received brentuximab vedotin. Patients who had received brentuximab vedotin were less likely than other patients to receive etoposide, methylprednisolone, cytarabine, and cisplatin (3 vs 13 patients) or a gemcitabine-based regimen (14 vs 20 patients) and had fewer comorbidities as assessed by the hematopoietic cell transplant comorbidity index (median score, 0 vs 2). Brentuximab vedotin-treated patients were also more likely than other patients to have a CR at the time of RIC allo-HCT (28.9% vs 4.3%), and were less likely than other patients to develop Bearman grade 3/4 toxicity (0 patients vs 7 patients). Although no differences in efficacy or survival were statistically significant, brentuximab vedotin appeared to trend toward better outcomes as assessed by overall survival, PFS, relapse, and nonrelapse mortality.



**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 diagnostic marker

A clinically relevant marker: Screening for CD30 can assist with the differential diagnosis of CD30-expressing tumors.^{1,2} For example, one study reported a 39% increase in the reproducibility of lymphoma diagnosis when immunostaining for CD30 was performed in conjunction with morphological analysis.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}

A valuable prognostic indicator: In several types of non-Hodgkin lymphoma (NHL), high levels of CD30 expression are associated with poor 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 in certain tumors can therefore facilitate an accurate diagnosis and a risk-adapted approach to treatment.⁶⁻⁸

NCCN Guidelines® on testing*: In Hodgkin lymphoma (HL) and NHL, CD30 staining should be included as part of the diagnostic workup as outlined in the NCCN Guidelines. CD30 screening is considered essential for immunophenotyping and differential diagnosis of certain T-cell lymphomas and is recommended as part of the immunohistochemistry panel in HL.^{1,2}

**For more information
on CD30 expression
and downloadable
resources, visit
scienceofCD30.com.**

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SCIENCE OF  **CD30**
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FLIPI category. A comparison against the PRIMA trial indicated a higher response rate with R2-CHOP vs R-CHOP in these matched patients, with complete remission rates of 74% and 65%, respectively.^{3,13} A comparison of PET outcomes in 77 evaluated patients receiving R2-CHOP vs 77 matched patients receiving R-CHOP in the PET-FL trial also showed a higher response rate with R2-CHOP vs R-CHOP, with PET response rates (based on the Deauville criteria) of 83% and 74%, respectively.² In comparison, the chemotherapy-free combination of lenalidomide plus rituximab in previously untreated patients demonstrated CR rates of 72% to 95%.^{7,8}

Overall, 85% of patients completed the R2-CHOP induction regimen, although 40% of cycles included at least 1 lenalidomide dose reduction, particularly during the last cycle. Although the median interval between cycles remained 21 days, 26% of patients required cycle delays longer than 3 days, and 17% required delays exceeding 1 week.

R2-CHOP was associated with grade 4 neutropenia in 65% of patients, grade 3/4 thrombocytopenia in approximately 20% of patients, and febrile neutropenia in 7% of patients. The investigators noted that the hematologic toxicity of the regimen was similar to that observed with R-CHOP (Figure 8). The most common nonhematologic toxicities were peripheral neuropathy, rash, and diarrhea.

Dr Tilly concluded that this trial confirmed the safety of R2-CHOP and yielded a high CR rate, although survival data are immature. Moreover, the role of R2-CHOP will also depend on outcomes of ongoing trials evaluating lenalidomide plus rituximab as frontline treatment of patients with high-tumor burden follicular lymphoma.

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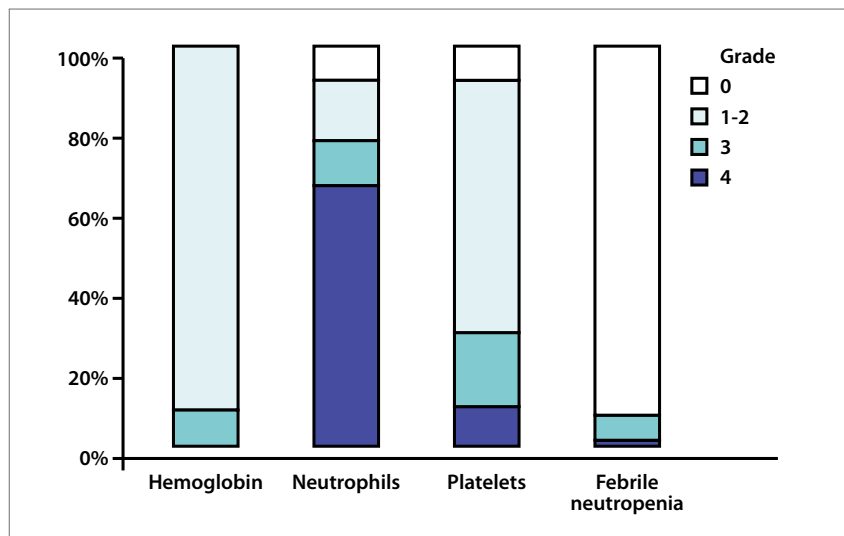


Figure 8. Hematologic toxicity in a phase 2 trial of lenalidomide in combination with R-CHOP in patients with high-burden follicular lymphoma. R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. Adapted from Tilly H et al. ASH abstract 248. *Blood*. 2013;122(21 suppl).¹²

ABSTRACT SUMMARY The RiBVD Regimen (Rituximab IV, Bendamustine IV, Velcade SC, Dexamethasone IV) Offers a High Complete Response Rate in Elderly Patients With Untreated Mantle Cell Lymphoma. Preliminary Results of the Lysa Trial “Lymphome Du Manteau 2010 SA”

Dr Remy Gressin presented preliminary results of a prospective phase 2 study evaluating a combination of rituximab, bendamustine, subcutaneous bortezomib, and intravenous dexamethasone (RiBVD) in older patients with previously untreated mantle cell lymphoma (Abstract 370). The study enrolled 70 evaluable patients, with a median age of 72 years (range, 64-83 years); 69% of patients had a high MIPI score. Patients received RiBVD every 4 weeks for up to 6 cycles. After 4 cycles, RiBVD was associated with an ORR of 87%, including 60% confirmed or unconfirmed CRs. Among the 69 patients with available PET data, 39 patients (57%) attained PET negativity, and 21 patients remained PET-positive. Subsequent analyses will determine whether this response rate translates into an improvement in PFS compared with overall historical data associated with other regimens. Common grade 3/4 hematologic toxicities included neutropenia (46%), thrombocytopenia (35%), anemia (7%), and febrile neutropenia (7%). The most common nonhematologic grade 3/4 toxicities were fatigue (14%) and neuropathy (13%). One treatment-related death was reported. Of the 16 patients who developed grade 2 or 3 neuropathy, 14 cases occurred after cycle 3; neuropathy was reversible in 11 patients. There was no correlation between age and the incidence of neuropathy.

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Reduced-Intensity Conditioning (RIC) and Allogeneic Stem Cell Transplantation (allo-SCT) for Relapsed/Refractory Hodgkin Lymphoma (HL) in the Brentuximab Vedotin Era: Favorable Overall and Progression-Free Survival (OS/PFS) With Low Transplant-Related Mortality (TRM)

Reduced-intensity conditioning (RIC) regimens are widely used in allogeneic stem cell transplant (allo-SCT) for patients with relapsed/refractory Hodgkin lymphoma because they are associated with reduced transplant-related mortality as compared with conventional high-dose chemotherapy regimens.¹ However, the optimal RIC regimen has not been identified, and disease progression remains a significant challenge.² Regardless of the conditioning regimen used, achievement of a CR pretransplant is associated with a more favorable prognosis after transplant.

Dr Paolo Anderlini presented results of a study assessing the efficacy and safety of an RIC regimen of gemcitabine, fludarabine, and melphalan prior to allo-SCT in patients with relapsed/refractory Hodgkin lymphoma.³ The investigators also assessed the influence of brentuximab vedotin on posttransplant outcomes, as this agent has demonstrated activity prior to allo-SCT in patients with relapsed/refractory Hodgkin lymphoma.⁴ The use of gemcitabine, fluda-

rabine, and melphalan was selected based on the demonstrated activity and safety profile of fludarabine and melphalan as an RIC regimen,⁵ the significant activity of gemcitabine in Hodgkin lymphoma,⁶ and the demonstrated synergy of gemcitabine and fludarabine.⁷

The study enrolled 27 patients with relapsed/refractory Hodgkin disease. Their median age was 31 years (range, 20-46 years), and they had received a median of 4 prechemotherapy regimens (range, 2-10). The majority of patients (70%) had received a prior autologous

ABSTRACT SUMMARY Effective Treatment of Chemotherapy-Refractory Diffuse Large B-Cell Lymphoma With Autologous T Cells Genetically Engineered to Express an Anti-CD19 Chimeric Antigen Receptor

Anti-CD19-chimeric antigen receptor T cells were used in the successful treatment of patients with advanced B-cell malignancies (Abstract 168). The chimeric antigen receptor used in this study was encoded by a gammaretrovirus and incorporated the variable regions of an anti-CD19 antibody, part of CD28, and part of CD3-zeta. A mean of 70.5% of the infused T cells expressed the chimeric antigen receptor, and the infused cells produced cytokines and degranulated in a CD19-specific manner. Prior treatment with chemotherapy has been shown to enhance the activity of adoptively transferred T cells, and patients received cyclophosphamide plus fludarabine (25 mg/m² daily for 5 days) before a single infusion of anti-CD19-CAR-transduced T cells. Among 9 patients with DLBCL, 4 achieved a CR and 2 a PR. These responses were ongoing at the time of the presentation. All of the DLBCL patients were chemotherapy-refractory. Acute toxicities reported in this study included fever, hypotension, and delirium. They resolved within 3 weeks of the cell infusion.

Table 2. CR Rates According to Use of Brentuximab Vedotin in a Trial of RIC and Allo-SCT

	Brentuximab Vedotin–Treated n=14 n (%)	Brentuximab Vedotin–Naive n=13 n (%)	Total N=26 P Value
CRs before allo-SCT	11/14 (79)	6/13 (46)	0.12*
CRs after allo-SCT	12/14 (85)	11/13 (85)	Not significant

*Fisher's method.

Allo-SCT, allogeneic stem cell transplant; CR, complete response; RIC, reduced-intensity conditioning. Data from Anderlini P et al. ASH abstract 410. *Blood*. 2013;122(21 suppl).³

SCT, and the median time to progression after autologous SCT was 5 months (range, 1-68 months). Entering allo-SCT, 67% of patients had a CR or complete response, unconfirmed (CRu), and 33% had a partial response. Transplants were performed using matched related donors for 60% of patients and matched unrelated donors for 40%. Brentuximab vedotin had been administered pre-SCT in 52% of patients (n=14), and 26% (n=7) had received brentuximab vedotin as the last line of treatment prior to allo-SCT.

Patients received gemcitabine 800 mg/m² on day -7 before transplant, fludarabine 33 mg/m² on days -5 through -2, and melphalan 70 mg/m² on days -3 and -2. Thymoglobulin at 3 mg/kg was administered for matched unrelated and mismatched related donor transplants, and all patients received tacrolimus and low-dose methotrexate for graft-vs-host disease (GVHD) prophylaxis.

Of the 27 enrolled patients, 6 patients died during the follow-up period, including 3 who died within the first 100 days of transplant. Causes of death included disease progression (n=2), graft rejection (n=1), pneumonia (n=2), and respiratory failure (n=1), for a treatment-related mortality rate of 15%. After a median follow-up of 18 months (range, 4-55 months), 21 of 27 patients were alive. Acute (grade 2-4) and chronic GVHD developed in 19% and 39% of patients, respectively. Median overall survival and PFS had not yet been reached at the time of analysis. The median time to disease progression was 13 months (range, 2-22 months).

In an analysis according to brentuximab vedotin exposure, there was a nonsignificant trend toward a higher

pre-allo SCT CR rate in brentuximab vedotin–treated patients vs brentuximab vedotin–naive patients (79% vs 46%; $P=.12$), although CR rates post-allo SCT were 85% in both groups (Table 2). All 7 patients who received brentuximab vedotin as bridge therapy remained alive and in remission.

The combination of gemcitabine, fludarabine, and melphalan appeared to have higher rates of pulmonary toxicity (33%) and cutaneous toxicity (19%) compared with historical controls of fludarabine and melphalan alone in

patients with acute myeloid leukemia.⁸ However, other organs did not appear to be incrementally more affected by the addition of gemcitabine.

Notwithstanding the limitations of cross-study comparisons, the authors compared historical outcomes obtained with fludarabine and melphalan before the introduction of brentuximab vedotin to those from this trial. There was a trend toward more favorable outcomes, including longer PFS and a lower incidence of progressive disease, with the use of gemcitabine, fludarabine, and melphalan

ABSTRACT SUMMARY Phase 1/2 Study of Brentuximab Vedotin in Pediatric Patients With Relapsed Or Refractory (R/R) Hodgkin Lymphoma (HL) or Systemic Anaplastic Large-Cell Lymphoma (sALCL): Preliminary Phase 2 Data for Brentuximab Vedotin 1.8 Mg/Kg in the HL Study Arm

Dr Franco Locatelli presented results of an open-label, multicenter, phase 1/2 dose-escalation study evaluating brentuximab vedotin in pediatric patients (Abstract 4378). The previously presented phase 1 portion of the study demonstrated an acceptable safety profile and antitumor activity with brentuximab vedotin administered at 1.8 mg/kg every 3 weeks (Locatelli F et al. Abstract P132. *Haematologica*. 2013;98[suppl 2]). The phase 2 portion included patients ages 5 to 17 years with relapsed/refractory Hodgkin lymphoma or systemic ALCL. Patients received intravenous brentuximab vedotin at 1.8 mg/kg every 3 weeks for up to 16 cycles. The study has enrolled 16 patients with Hodgkin lymphoma (median age, 15 years; range, 8-18 years) who received brentuximab vedotin for a median of 4.5 cycles (range, 1-16). The most common treatment-emergent adverse events were nausea, pyrexia, and paresthesia. Three patients developed 4 serious adverse events at least grade 3 in severity that were considered study drug–related; they included hepatotoxicity and febrile neutropenia (n=1), pneumonia (n=1), and anaphylactic reaction (n=1). Two patients discontinued treatment owing to adverse events, which included hepatotoxicity and peripheral neuropathy, and 1 patient died of cardiac arrest. Pharmacokinetic analysis showed that serum concentrations of brentuximab vedotin and MMAE peaked as expected and brentuximab vedotin was detectable just prior to each subsequent infusion, indicating sustained exposure. Preliminary efficacy analysis indicated activity of brentuximab vedotin, with 7 of 15 evaluable patients (47%) attaining an objective response (47%), including 5 of 15 (33%) with a CR. The phase 2 study is ongoing to assess responses to brentuximab vedotin in pediatric patients with systemic ALCL.

in the brentuximab vedotin era.⁵ These improvements were observed even after controlling for the higher pretransplant CR rates now reported.⁵

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Combination Biologic Therapy Without Chemotherapy as Initial Treatment for Mantle Cell Lymphoma: Multi-Center Phase II Study of Lenalidomide Plus Rituximab

Currently, the optimal regimen for the initial treatment of mantle cell lymphoma has not been determined. Multiple studies have been undertaken in recent years to identify the best approach. In general, regimens based on currently available biologic agents in combination with chemotherapy do not result in a cure. Moreover, in selected patients with asymptomatic mantle cell lymphoma, initial treatment can be deferred without detrimentally affecting survival.¹

Numerous novel agents have been evaluated in the treatment of mantle cell lymphoma, including the immunomodulatory agent lenalidomide, which demonstrated efficacy in relapsed/refractory mantle cell lymphoma as monotherapy and in combination with rituximab.^{2,3} Based on the demonstrated efficacy of these biologic agents in mantle cell lymphoma, a multicenter phase 2 study was undertaken evaluating a nonchemotherapy induction regimen of rituximab plus lenalidomide for the initial treatment of mantle cell lymphoma.⁴ The regimen consisted of rituximab at 375 mg/m² administered for 4 weekly doses in cycle 1, followed

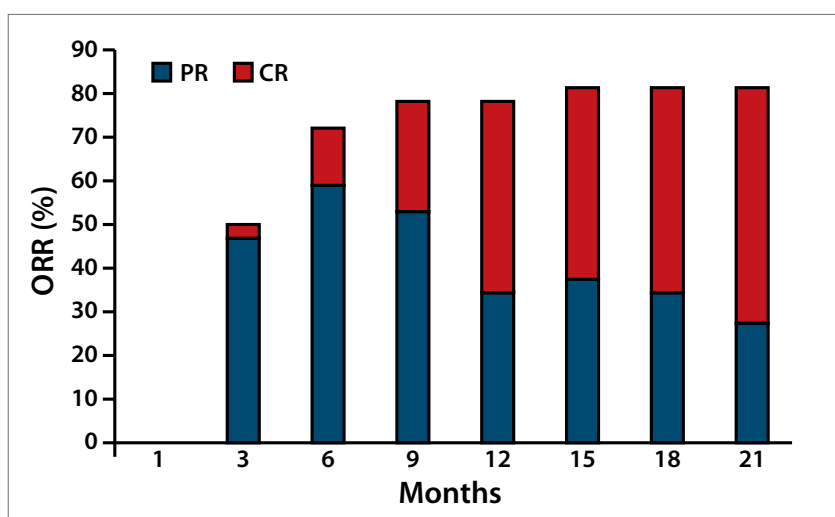


Figure 9. In a multicenter, phase 2 trial of lenalidomide plus rituximab, responses improved over time. CR, complete response; ORR, overall response rate; PR, partial response. Adapted from Ruan J et al. ASH abstract 247. *Blood.* 2013;122(21 suppl).⁴

by administration every 2 months for 12 months, plus lenalidomide at 20 mg (up to 25 mg) administered on days 1 to 21 every 28 days. After 12 cycles, patients without disease progression received a maintenance regimen of rituximab at 375 mg/m² administered every 8 weeks plus lenalidomide at 15 mg on days 1 to 21 every 28 days, which was continued until disease progression.

The study enrolled 32 patients with a median age of 65 years (range, 42-86 years); 76% were male, 97% had an ECOG performance status of 0 to 1, and 66% had a low or intermediate Mantle Cell Lymphoma International Prognostic Index (MIPI). The remaining 34% of patients with a high MIPI score were enrolled based on ineligibility for, or refusal of, conventional

ABSTRACT SUMMARY A Phase III Study of Enzastaurin in Patients With High-Risk Diffuse Large B Cell Lymphoma Following Response to Primary Treatment: the PRELUDE Trial

In patients with high-risk DLBCL in first remission, postinduction therapy with the protein kinase C (PKC) β inhibitor enzastaurin does not appear to confer an efficacy benefit, according to results of the randomized, phase 3 PRELUDE (Preventing Relapse in Lymphoma Using Daily Enzastaurin) trial (Abstract 371). The trial enrolled 758 patients with high-risk DLBCL in first remission following induction therapy with R-CHOP. Patients were randomly assigned to oral enzastaurin administered at 500 mg daily with a loading dose of 1125 mg on day 1 (n=504), or oral placebo administered once daily (n=254), each for 3 years. There was no significant difference between enzastaurin and placebo as assessed by disease-free survival, event-free survival, or overall survival at 2 or 4 years. The cell of origin did not affect disease-free survival outcomes, and subset analyses did not identify any patient population for which enzastaurin had a significant benefit. Toxicities were similar to those reported in other clinical trials of enzastaurin, with the most frequent treatment-related adverse events consisting of chromaturia (18.5%), prolonged QT interval (10.8%), and diarrhea (10.3%). There was no significant difference in the incidence of grade 3 or higher adverse events between the arms.

chemotherapy. Lactate dehydrogenase levels were elevated in 40% of patients, and bone marrow involvement was present in 88% of patients. Indications for treatment included symptomatic lymphadenopathy (44%), cytopenias (22%), bulky disease (≥ 5 cm; 16%), gastrointestinal symptoms or bleeding (9%), patient preference (6%), or a rap-

idly increasing white blood cell count exceeding 100,000/mm³ (3%).

In the intent-to-treat population, lenalidomide plus rituximab was associated with an ORR of 81%, including 53% CRs. Two patients discontinued therapy after tumor flares that occurred during treatment cycle 1. Among the 30 evaluable patients, the ORR was 87%,

including 57% CRs. The median time to partial response and CR was 3 months and 11 months, respectively. Responses improved over time (Figure 9). After a median follow-up of 16 months, the 12-month PFS rate was 93%. All patients were alive at the time of the analysis.

The most common grade 3 or higher hematologic adverse events were neutropenia (47%), thrombocytopenia (16%), and anemia (6%). Grade 3 or higher nonhematologic adverse events reported in at least 5% of patients included rash (22%), fatigue (9%), tumor flare (9%), and infusion reaction (6%).

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Commentary

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Lymphoma abstracts presented at the 2013 American Society of Hematology meeting focused on new drugs, either as single agents or in combination with standard regimens. Encouragingly, many of these new agents appear to have activity in several different lymphoma subtypes and offer new options to patients with relapsed and refractory disease. Efforts to incorporate new agents into earlier lines of therapy are also under way.

DLBCL

I presented interim results for patients with relapsed diffuse large B-cell lymphoma (DLBCL) and other B-cell lymphomas from a phase 2 trial of brentuximab vedotin.¹ Approximately 14% to 25% of large B-cell lymphomas express CD30, although usually at much lower levels than patients with Hodgkin lymphoma or anaplastic large cell lymphoma.^{2,3} The brentux-

imab vedotin single-agent response rate of 42% in patients with relapsed/refractory DLBCL, including transformed large cell, is quite encouraging and somewhat surprising given the very low level of CD30 expression in the majority of responders. Although responses were not durable in most patients, the response rate and favorable toxicity profile justifies further investigation of brentuximab vedotin in patients with CD30-positive

DLBCL, perhaps in combination with other agents, as initial treatment or in first-line salvage regimens. Efforts to explore the mechanisms of response to brentuximab vedotin in DLBCL, which is CD30-negative by routine immunohistochemistry, are under way.

Investigators from the National Cancer Institute presented remarkable results in 9 patients with refractory DLBCL using autologous T cells genetically engineered to express an anti-CD19 chimeric antigen receptor.⁴ This approach was first reported in patients with refractory chronic lymphocytic leukemia or acute lymphoblastic leukemia but also appears to hold promise for DLBCL. Of the 9 patients treated, 4 achieved a complete response and 2 a partial response, all of which were ongoing at the time of the presentation (range, 2-22+ months). Most patients experienced acute toxicities related to cytokine release syndrome, which were self-limited. Larger, multicenter trials are in development.

Two trials were presented combining new agents with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in frontline therapy of DLBCL: a phase 2 trial adding lenalidomide⁵ and a phase 1b trial with ibrutinib.⁶ Both agents have shown single-agent activity in relapsed/refractory non-germinal center DLBCL. Both regimens were well tolerated and resulted in high overall and complete response rates. Phase 3 trials of both regimens compared to R-CHOP are actively accruing and may provide improved outcomes for the subset of high-risk DLBCL patients with an activated B-cell phenotype.

Follicular Lymphoma

Lenalidomide in combination with R-CHOP was examined in a phase 2 trial of patients with high-tumor burden follicular lymphoma.⁷ This regimen had high overall and complete response rates, similar to results seen with other regimens, including rituximab/bendamustine and rituximab/

lenalidomide.^{8,9} Given the increased myelosuppression, peripheral neuropathy, and risk of cardiac toxicity with R-CHOP compared with other regimens, many oncologists do not use it as the initial treatment of follicular lymphoma, unless there is a concern about transformation. This trial is therefore of limited relevance.

In a randomized phase 2 study comparing consolidation with ibritumomab tiuxetan vs maintenance with rituximab following R-CHOP in patients with follicular lymphoma, progression-free survival (PFS) was longer in patients who received maintenance rituximab therapy.¹⁰ Results of this study will not impact the current standard of care in follicular lymphoma. Despite the fact that the PRIMA (Primary Rituximab and Maintenance) study showed an improvement in PFS only and not in overall survival with maintenance rituximab,¹¹ most patients with follicular lymphoma now receive maintenance rituximab following rituximab/chemotherapy induction. Whether there is a role for both maintenance rituximab and consolidation with ibritumomab tiuxetan is unknown. Also limiting the applicability of these results is the change of induction to rituximab/bendamustine

for the majority of patients with newly diagnosed follicular lymphoma. The use of ibritumomab tiuxetan after bendamustine induction has never been studied and could potentially result in higher rates of myelodysplastic syndrome than were seen with either agent alone. This approach is not recommended outside the setting of a clinical trial.

Not unexpectedly, following induction with single-agent rituximab, prolonged maintenance with rituximab (5 years) resulted in improved PFS rates when compared with 4 total doses of maintenance rituximab over 8 months, as reported in the phase 3 SAKK (Swiss Group for Clinical Cancer Research) trial.¹² There was no improvement in overall survival. Previous results of the RESORT (Rituximab Extended Schedule or Retreatment Trial) study comparing indefinite maintenance to re-treatment following rituximab induction showed no significant advantage to maintenance with regard to time to requiring chemotherapy.¹³ Re-treatment at relapse represented a substantial cost savings compared with prolonged maintenance and has no survival disadvantage. The SAKK trial is unlikely to affect standard practices in the treatment of follicular lymphoma.

ABSTRACT SUMMARY Final Results of Phase II Study of Lenalidomide Plus Rituximab-CHOP21 in Elderly Untreated Diffuse Large B-Cell Lymphoma Focusing on the Analysis of Cell of Origin: REAL07 Trial of the Fondazione Italiana Linfomi

Treatment in the phase 2 REAL07 (Revlimid in Elderly Aggressive Lymphoma) trial consisted of R-CHOP21 plus 15 mg of lenalidomide on days 1 to 14 for 6 courses (Abstract 850). Among the 49 patients enrolled, ORR was 92% (86% CRs and 6% PRs). Three patients (6%) did not respond, and 1 (2%) died of homicide. At a median follow-up of 28 months, 2-year overall survival was 92% (95% CI, 79-97), 2-year PFS was 80% (95% CI, 64-89), and 2-year EFS was 70% (95% CI, 55-81). The 2-year PFS was 89% for patients with a low-intermediate IPI, 76% for those with an intermediate-high IPI, and 72% for those with a high IPI. Toxicities were mild. Cell of origin analysis was reported according to immunohistochemistry data. Clinical characteristics between germinal center B (GCB; 16 patients) and non-GCB (16 patients) were superimposable, except that most patients in the non-GCB group had a high IPI. ORR was 88% for both groups. At a median follow-up of 28 months, the 2-year PFS was 71% in the GCB-group and 81% in the non-GCB group.

ALCL

A study presented by Dr Sara Redaelli of crizotinib showed a remarkable response rate of 100% in relapsed anaplastic lymphoma kinase (*ALK*)-positive anaplastic large cell lymphoma (ALCL).¹⁴ This finding warrants further investigation of crizotinib in previously untreated ALCL, initially in combination with active regimens. As in trials of crizotinib in lung cancer,¹⁵ patients with *ALK*-positive ALCL appear to develop *ALK* kinase domain mutations leading to relapse. Next-generation *ALK* inhibitors with enhanced activity against *ALK* mutations may eventually provide yet another option for relapsed *ALK*-positive ALCL.

Long-term follow-up of brentuximab vedotin in relapsed ALCL continues to show a subset of patients who remain in remission more than 3 years after completion of therapy. Dr Barbara Pro presented an analysis of patients who had achieved a complete response with brentuximab vedotin in an ongoing phase 2 trial.^{16,17} PFS was longer in complete-response patients who went on to receive stem cell transplant (SCT) than in patients who did not undergo post-treatment SCT. However, there was no difference in overall survival between the 2 groups, and many patients relapsing after achieving a complete response were successfully re-treated with brentuximab vedotin. The development of brentuximab vedotin for relapsed ALCL has dramatically changed the prognosis for patients with this historically refractory disease, with a 3-year overall survival rate of 63%. Whether transplant is necessary for those achieving complete response with brentuximab vedotin is unclear.

A multicenter, open-label phase 1 study of brentuximab vedotin administered sequentially with chemotherapy or in combination with chemotherapy (CHOP without vincristine) in patients with ALCL and other newly diagnosed CD30-positive mature (peripheral) T-cell lymphomas showed a 1-year PFS of 77%.¹⁸ Unfortunately, remission duration beyond 1 year was not

assessed as part of this study. Although the 1-year PFS appears encouraging, longer follow-up is needed to draw conclusions about the potential advantage of this regimen compared with standard therapy. The single-agent response rate of 87% in relapsed ALCL certainly justifies evaluation of brentuximab vedotin in first-line therapy. The ongoing phase 3 study of CHOP vs CHOP without vincristine and brentuximab vedotin will define the role of brentuximab vedotin as initial therapy.¹⁹

Mantle Cell Lymphoma

A small phase 2 study of rituximab and lenalidomide as first-line therapy for mantle cell lymphoma introduced a nonchemotherapy option for this often older population.²⁰ The protocol was initially intended for “low-risk” mantle cell lymphoma, but one-third of the patients had a high-risk Mantle Cell Lymphoma International Prognostic Index (MIPI) score. The reported 1-year PFS of 93% is unprecedented, even with aggressive approaches, including stem cell transplant. It is possible that

selection bias contributed to these remarkably favorable results. If longer follow-up confirms durable responses, this regimen should be studied in larger and more diverse patient populations. The recent approval by the US Food and Drug Administration (FDA) of ibrutinib, a Bruton's tyrosine kinase inhibitor, for relapsed mantle cell lymphoma has stimulated interest in evaluating this drug in first-line therapy of mantle cell lymphoma. Studies comparing nonchemotherapy approaches with more aggressive approaches are warranted. With new highly effective and well-tolerated agents for mantle cell lymphoma, the standard of care for initial therapy should be reexamined.

The current standard of care for initial treatment of mantle cell lymphoma is bendamustine/rituximab followed by maintenance rituximab. A phase 2 trial of rituximab, bendamustine, subcutaneous bortezomib, and intravenous dexamethasone (RiBVD) added bortezomib on days 1, 4, 8, and 11, and a single dose of dexamethasone on day 2 of each cycle of standard-dose bendamustine/rituximab.²¹ The response rates were simi-

ABSTRACT SUMMARY Brentuximab Vedotin Administered to Platinum-Refractory Transplant Naïve Hodgkin Lymphoma Patients Can Increase the Proportion Achieving FDG-PET Negative Status

A retrospective study demonstrated the ability of brentuximab vedotin to induce responses in patients with relapsed/refractory Hodgkin lymphoma that is persistently fluorodeoxyglucose (FDG)/PET-positive after salvage platinum-based regimens prior to ASCT (Abstract 2106). Among the 16 patients included in the analysis (median age, 30 years; range, 16-64 years), 69% had primary refractory disease. The best response to prior chemotherapy was partial response in 38% and CR in 12%. Patients received a median of 4 cycles of brentuximab vedotin administered at 1.8 mg/kg every 3 weeks. The ORR as assessed by FDG/PET was 50%, including 44% with CRs. Fourteen patients (88%) proceeded to high-dose chemotherapy and ASCT, which resulted in a CR in 8 patients (73%) and a partial response in 1 patient (9%). FDG/PET-negative responses to brentuximab vedotin were observed in 50% of patients (2 of 4) with a partial response to platinum-based salvage chemotherapy and 56% of patients (5 of 9) with stable disease after platinum-based salvage chemotherapy. No FDG-PET-negative responses were observed in the 3 patients with disease progression after platinum-based therapy. Based on these findings, the investigators suggested that brentuximab vedotin may be particularly effective for patients with at least stable disease following prior regimens.

lar to those reported with bendamustine/rituximab.²² An ongoing phase 3 cooperative group trial (E1411) in patients with previously untreated mantle cell lymphoma is evaluating several regimens: rituximab plus bendamustine, followed by rituximab consolidation; rituximab, bendamustine, and bortezomib followed by rituximab consolidation; rituximab plus bendamustine, followed by lenalidomide plus rituximab consolidation; and rituximab, bendamustine, and bortezomib, followed by lenalidomide plus rituximab consolidation.²³

Indolent NHL

A phase 2 study presented by Dr Ajay Gopal evaluated idelalisib monotherapy in patients with previously treated indolent non-Hodgkin lymphoma that is refractory to both rituximab and an alkylating agent.²⁴ Idelalisib is one of several new drugs targeting the B-cell receptor pathway, many of which have shown exciting results in a variety of subtypes of B-cell lymphoma. Despite a “crowded market” for relapsed follicular lymphoma therapies, idelalisib’s single-agent response rate of 57% in patients refrac-

tory to alkylating agents and rituximab, in addition to the relatively favorable side effect profile, will hopefully result in FDA approval for this indication.

Hodgkin Lymphoma

A single-institution, phase 2 study in relapsed Hodgkin lymphoma showed encouraging preliminary results using brentuximab vedotin as second-line therapy in the pretransplant salvage setting.²⁵ Unfortunately, the single-agent complete response rate was only 29%, and the majority of patients had to undergo additional therapy with ifosfamide, carboplatin, and etoposide (ICE) chemotherapy pretransplant. Of note, the investigators used a very stringent definition of complete response, requiring a Deauville score of 1 with residual uptake less than or equal to the blood pool. Even if this approach results in only a third of patients avoiding aggressive salvage therapy prior to transplant, it would be beneficial. Additional trials combining brentuximab with ICE are in development. Further studies evaluating outcomes of patients achieving a Deauville score of 2, or perhaps

even 3, following brentuximab vedotin who proceed to transplant without further salvage would also be of interest.

Several small series,²⁶ including one presented by Dr Paolo Anderlini,²⁷ have reported favorable results with a reduced intensity conditioning regimen for allogeneic stem cell transplant in patients with relapsed Hodgkin lymphoma who have failed a prior autologous transplant. Gemcitabine was added to the preparative regimen, possibly accounting for the increased pulmonary toxicity that was seen with this regimen. Transplant-related mortality was 15%, and moderate-to-severe chronic graft-vs-host disease occurred in 39%, likely impacting quality of life. A small subset of Hodgkin lymphoma patients treated with brentuximab vedotin following relapse after an autologous transplant will have a durable response. Two potential approaches for complete responders to brentuximab vedotin would be for them to proceed to a reduced intensity conditioning regimen allogeneic stem cell transplant or for them to undergo observation until relapse, with the plan to re-treat with brentuximab vedotin and then consider a reduced intensity conditioning regimen allogeneic stem cell transplant after brentuximab vedotin re-treatment.

With standard therapy, older patients with Hodgkin lymphoma have worse outcomes than younger patients, and age is an independent risk factor in most prognostic models. Advanced stage is more common in older patients, and concurrent cardiopulmonary disease often limits the use of standard doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy. In this phase 2 trial, older Hodgkin lymphoma patients receiving brentuximab vedotin achieved an overall response rate of 89% and a complete response rate of 63%.²⁸ Single-agent brentuximab vedotin should be further explored in first-line therapy. Information regarding the durability of the complete responses and the ability to convert partial responses to complete responses with standard chemotherapy

ABSTRACT SUMMARY Rituximab Maintenance Treatment for a Maximum of 5 Years in Follicular Lymphoma: Results of the Randomized Phase III Trial SAKK 35/03

In the randomized phase 3 SAKK (Swiss Group for Clinical Cancer Research) 35/03 trial, extending maintenance rituximab in patients with follicular lymphoma significantly lengthened PFS (Abstract 508). The trial randomly assigned 165 patients with follicular lymphoma with responses to rituximab induction therapy to maintenance rituximab administered every 2 months for 4 doses (n=82) or every 2 months for up to 5 years (n=83). In the overall analysis, there was no significant difference in event-free survival (EFS) with long-term maintenance therapy vs short-term maintenance (median EFS, 5.3 vs 3.4 years; $P=.14$), which the investigators attributed to superior outcomes in the short-term arm during the initial study period, when the 2 arms were receiving the same treatment. A subsequent retrospective analysis that limited the EFS analysis to events occurring after the treatment arms were different showed a statistically significant improvement in EFS with long-term maintenance therapy, with a median EFS of 7.1 years vs 2.9 years with short-term therapy ($P=.004$). The PFS analysis also favored long-term over short-term therapy, with a median PFS of 7.4 years and 3.5 years, respectively (hazard ratio, 0.63; 95% CI, 0.41-0.99; $P=.04$). The investigators reported no substantial increase in toxicity with the use of long-term rituximab maintenance.

following brentuximab vedotin will be essential to better assess this approach.

Updated results from the pivotal phase 2 study of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma after autologous stem cell transplant have confirmed the overall survival seen in previous reports.^{29,30} Approximately 10% to 15% of patients achieve prolonged remissions, and perhaps even “cures,” following single-agent brentuximab vedotin despite failing a previous autologous transplant.

A phase 1 trial in relapsed/refractory Hodgkin lymphoma of panobinostat and ICE showed an overall response rate of 86% and a complete response rate of 71%.³¹ This complete response rate is significantly higher than in previous reports.³² However, this study enrolled a small number of patients from a single institution, and therefore, the comparison is limited. Unfortunately, panobinostat was not approved by the FDA for use in Hodgkin lymphoma, hampering its further development in this disease.

A small, phase 1/2 study examined brentuximab vedotin in pediatric patients with relapsed or refractory Hodgkin lymphoma or systemic anaplastic large cell lymphoma.³³ The pharmacokinetics and toxicity of brentuximab vedotin seen in children appear similar to those seen in phase 1/2 studies in adults. The small patient numbers in this study preclude comparison of response rates to brentuximab vedotin in pediatric and adult patients with relapsed Hodgkin lymphoma.

Cutaneous T-Cell Lymphoma

Despite the development of new drugs for mycosis fungoides over the last decade, better treatment options for patients with advanced-stage disease are needed. Given the high risk of infection owing to skin breakdown, nonmyelosuppressive treatments, such as brentuximab vedotin, are preferred. Dr Madeleine Duvic presented results of a phase 2 trial of brentuximab vedotin for CD30-positive cutaneous T-cell lymphomas

and lymphoproliferative disorders.³⁴ The overall response rate was 73% in all disease types, and 54% in patients with mycosis fungoides. Unfortunately, most of the responses with brentuximab vedotin were transient, with patients relapsing on or shortly after treatment discontinuation. Continued administration schedules may be feasible using lower doses and longer cycle lengths. This study of brentuximab vedotin is the first to include patients with lymphomatoid papulosis, and the high response rates are encouraging. Although these patients often respond to low-dose weekly methotrexate, a subset will have frequent symptomatic lesions, and brentuximab vedotin represents a potential option for this group.

Acknowledgment

Dr Bartlett has received clinical trial research funding from Seattle Genetics, Pharmacyclics, Janssen, Celgene, Genentech, Novartis, and Pfizer. She is a member of the Advisory Board for Seattle Genetics.

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ABSTRACT SUMMARY Three-Year Follow-Up Data and Characterization of Long-Term Remissions From an Ongoing Phase 2 Study of Brentuximab Vedotin in Patients With Relapsed or Refractory Hodgkin Lymphoma

Dr Ajay Gopal presented updated results from the pivotal phase 2 study of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma after autologous stem cell transplantation (Abstract 4382). After a median follow-up of 33 months since the first dose of brentuximab vedotin, 51 of 102 patients (50%) remained alive, with a median overall survival of 40.5 months and an estimated 3-year overall survival rate of 54%. The median PFS by central independent review was 5.6 months overall and 9.0 months among patients with an objective response. As of the last analysis, 18 patients were considered to be still in remission per investigator review and 14 were considered to be in remission as assessed by central independent review. Consolidative allogeneic stem cell transplantation was completed after brentuximab vedotin in 5 of these 14 patients, with the remaining 9 patients having received no further treatment after brentuximab vedotin. Additional studies are assessing the efficacy and safety of brentuximab vedotin in other settings, including a randomized, phase 3 study evaluating brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine vs doxorubicin, bleomycin, vinblastine, and dacarbazine for the initial treatment of Hodgkin lymphoma.

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ABSTRACT SUMMARY Brentuximab Vedotin Administered Before, During, and After Multi-Agent Chemotherapy in Patients (pts) With Newly-Diagnosed CD30+ Mature T- and NK-Cell Lymphomas

Dr Michelle Fanale reported results of a multicenter, open-label phase 1 study evaluating the safety, dosing, and antitumor activity of brentuximab vedotin administered sequentially with chemotherapy or in combination with chemotherapy in 39 patients with CD30-positive mature (peripheral) T-cell lymphomas, including 32 patients with systemic ALCL (Abstract 4386). A total of 13 patients received sequential treatment consisting of 2 cycles of brentuximab vedotin administered at 1.8 mg/kg every 3 weeks followed by CHOP (11 patients completed 6 cycles); 12 patients subsequently received maintenance single-agent brentuximab vedotin. The only serious adverse event occurring in more than 1 patient was febrile neutropenia, reported in 2 patients. The incidence of brentuximab vedotin dose delays and reductions was 6% and 22%, respectively. After a median follow-up of 24 months from the first dose, the estimated 1-year PFS and overall survival rates were 77% and 85%, respectively. A total of 26 patients received combination treatment, which consisted of brentuximab vedotin administered in combination with CHP (CHOP without vincristine), followed by maintenance brentuximab vedotin in 81% of patients. The most common serious adverse events were febrile neutropenia (31%), pyrexia (8%), and cardiac failure (8%). The incidence of brentuximab vedotin dose delays and reductions was 7% and 13%, respectively. Overall, the combination approach was associated with an ORR of 100%, including 88% CR. After a median follow-up of 21 months from the first dose, the estimated 1-year PFS and overall survival rates were 71% and 88%, respectively. Based on the demonstrated activity and safety profile of brentuximab vedotin, an ongoing phase 3 trial is comparing brentuximab vedotin plus CHP vs CHOP alone in the initial treatment of patients with CD30-positive mature T-cell lymphomas.

Leaders in antibody-drug conjugate development

Extending the reach of our technology through collaboration

Company

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Millennium: The Takeda Oncology Company

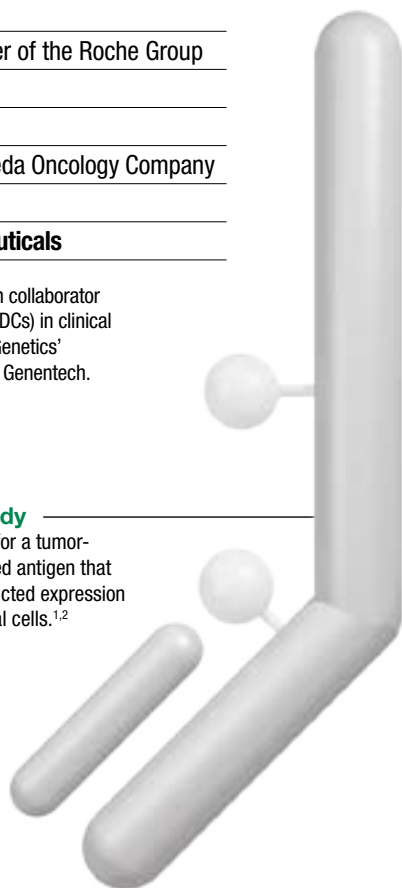
Pfizer

Progenics Pharmaceuticals

There are more than a dozen collaborator antibody-drug conjugates (ADCs) in clinical development using Seattle Genetics' technology, including 8 from Genentech.

Antibody

Specific for a tumor-associated antigen that has restricted expression on normal cells.^{1,2}



Empowering antibodies by linking precision with potency

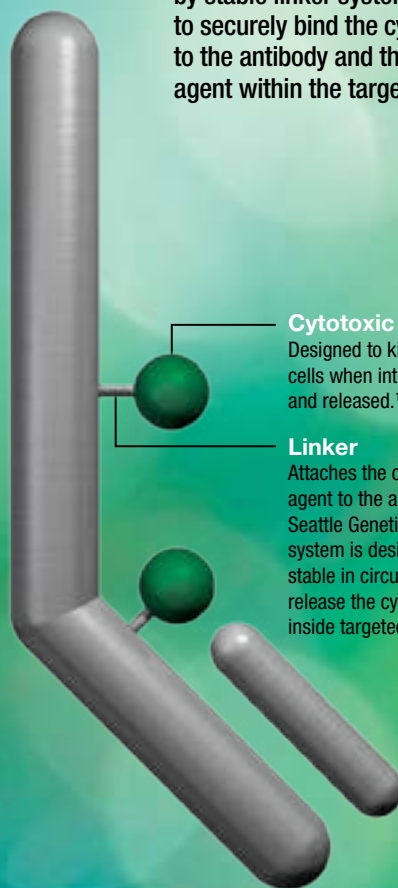
Seattle Genetics has developed proprietary, industry-leading technology that employs a monoclonal antibody specific for a tumor-associated antigen, plus potent cytotoxic agents connected by stable linker systems designed to securely bind the cytotoxic agent to the antibody and then release the agent within the targeted cell.

Cytotoxic agent

Designed to kill target cells when internalized and released.^{1,2}

Linker

Attaches the cytotoxic agent to the antibody. Seattle Genetics' linker system is designed to be stable in circulation and release the cytotoxic agent inside targeted cells.¹⁻³



In addition to licensing its ADC technology, Seattle Genetics is developing 7 proprietary ADCs. The company's robust pipeline of empowered antibody-based therapies and one approved ADC are designed to address significant unmet medical needs.



For more information about our ADC technology and to download an educational slide deck, please visit seattlegenetics.com/technology.

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