Clinical Advances in HEMATOLOGY & ONCOLOGY A Peer-Reviewed Journal

September 2013

Volume 11, Issue 9, Supplement 14

A SPECIAL MEETING REVIEW EDITION

Highlights in Lymphoma From the 12th International Conference on Malignant Lymphoma

A Review of Selected Presentations From the 12th International Conference on Malignant Lymphoma

June 19-22, 2013 • Lugano, Switzerland

Special Reporting on:

- PET-Adapted Sequential Therapy With Brentuximab Vedotin and Augmented-ICE Induces FDG-PET Normalization in 92% of Patients With Relapsed and Refractory Hodgkin Lymphoma
- Interim Results From a Phase II Study of PI3K-Delta Inhibitor Idelalisib in Patients With Relapsed Indolent Non-Hodgkin Lymphoma Refractory to Both Rituximab and an Alkylating Agent
- Progression-Free Survival Analyses of Two Pivotal Phase 2 Studies of Brentuximab Vedotin in Patients With Relapsed or Refractory Hodgkin Lymphoma or Systemic Anaplastic Large-Cell Lymphoma
- A Phase II Trial of Response-Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging: U.S. Intergroup S0816
- Safety and Efficacy of Brentuximab Vedotin for the Treatment of Relapsed or Refractory Mature T-/NK-Cell Lymphomas
- Phase I Study of the Anti-CD22 Antibody-Drug Conjugate DCDT2980S With or Without Rituximab in Patients With Relapsed or Refractory B-Cell Non-Hodgkin's Lymphoma
- Single-Agent Ibrutinib (PCI-32765) Is Highly Effective in Chronic Lymphocytic Leukemia (CLL) Patients With 17p Deletion
- Updated Results of a Phase I First-in-Human Study of the BCL-2 Inhibitor ABT-199 (GDC-0199) in Patients With Relapsed/ Refractory (R/R) Chronic Lymphocytic Leukaemia (CLL)
- · Objective Responses in Relapsed or Refractory B-Cell Lymphomas With Single-Agent Brentuximab Vedotin
- Phase I Study of the Anti-CD79b Antibody-Drug Conjugate DCDS4501A in Relapsed or Refractory B-Cell Non-Hodgkin's Lymphoma
- Preliminary Safety and Efficacy of IPI-145, a Potent Inhibitor of Phosphoinositide-3-Kinase-δ,-g, in Patients With Relapsed/ Refractory B-Cell Lymphoma

PLUS Meeting Abstract Summaries

With Expert Commentary by:

Craig 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

ON THE WEB: hematologyandoncology.net

Indexed through the National Library of Medicine (PubMed/MEDLINE), PubMed Central (PMC), and EMBASE

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}

* Referenced with permission from The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Hodgkin's Lymphoma V.2.2012 and Hodgkin Lymphoma V.2.2012. @ 2012 National Comprehensive Cancer Network, Inc. All rights reserved. Accessed June 20, 2012. To view the most recent and complete version of the guideline, go online to www.nccn.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

References: 1. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Hodgkin lymphoma (version 2.2012). Fort Washington, PA: NCCN; 2012. 2. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: non-Hodgkin's lymphomas (version 2.2012). Fort Washington, PA: NCCN; 2012. 3. The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group Classification of Non-Hodgkin's Lymphoma. *Blood*. 1997;89(11):3903-3918. 4. Ulbright TM. Germ cell tumors of the gonads: a selective review emphasizing problems in differential diagnosis, newly appreciated, and controversial issues. *Mod Pathol*. 2005;18(suppl 2):S61-S79. 5. Lau SK, Weiss LM, Chu PG. D2-40 immunohistochemistry in the differential diagnosis of seminoma and embryonal carcinoma: a comparative immunohistochemical study with KIT (CD117) and CD30. *Mod Pathol*. 2007;20(3):320-325. 6. Savage KJ, Harris NL, Yose M, et al; International Peripheral T-Cell Lymphoma Project. ALK: anaplastic large-cell ymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-Cell Lymphoma and the repriser and primary cutaneous anaplastic large cell lymphomas. *Semin Hematol*. 2003;40(3):244-256. 8. Camacho FI, Bellas C, Corbacho C, et al. Improved demonstration of immunohistochemical prognostic markers for survival in follicular lymphoma cells. *Mod Pathol*. 2011;74(5):688-707.

on CD30 expression and downloadable resources, visit scienceofCD30.com.

For more information

SeattleGenetics®

Seattle Genetics and $\overleftarrow{\mathbf{v}}$ are US registered trademarks of Seattle Genetics, Inc. © 2012 Seattle Genetics, Inc., Bothell, WA 98021 All rights reserved. Printed in USA US/BVP/2012/0072 SCIENCE OF Advancing the understanding of CD30 in disease

PET-Adapted Sequential Therapy With Brentuximab Vedotin and Augmented-ICE Induces FDG-PET Normalization in 92% of Patients With Relapsed and Refractory Hodgkin Lymphoma

arly studies at Memorial Sloan-Kettering Cancer Cen-✓ ter have identified 3 important risk factors for patients who have failed their frontline treatment for Hodgkin lymphoma (HL): the presence of B symptoms at the time of relapse, the presence of extranodal sites of disease, and a duration of remission of less than 1 year. For the past 15 years, sequential trials have administered risk-adaptive therapy based on the presence or absence of these risk factors. For example, patients with 0 to 1 risk factors have received standardized chemotherapy, whereas patients with 2 or more risk factors have received augmented ifosfamide, carboplatin, and etoposide (ICE) chemotherapy. This approach has improved the outcome for poorrisk patients, likely by increasing their chemosensitivity and allowing more patients to progress to transplant.

A combined analysis of patients followed prospectively on 3 consecutive protocols at Memorial Sloan-Kettering Cancer Center found that the most important prognostic factor was whether or not the patients were able to normalize their functional imaging.¹ That study included patients who had gallium scans and a minority of patients who had positron emission tomography (PET) scans.

Data regarding the prognostic factors prompted the current study. Patients received risk-adapted ICEbased chemotherapy and were evaluated by PET scan. Those with a normalized PET scan went on to an autotransplant. Those who had persistent abnormalities on their PET scan received additional non–cross-resistant therapy with gemcitabine, vinorelbine, and doxorubicin.²

Both patients whose PET scans normalized after ICE chemotherapy and patients whose PET scan normalized after ICE followed by treatment with gemcitabine, vinorelbine, and doxorubicin had good outcomes, and outcomes were similar. These findings suggest that the goal of salvage chemotherapy is to normalize the PET scan, and it does not matter how the patient arrives there.

No one standard salvage regimen exists. Common regimens include ICE, dexamethasone, cytarabine, and cisplatin (DHAP), and gemcitabinebased therapy. These regimens tend to be immunosuppressive and require hospitalization. Brentuximab vedotin is very well-tolerated and very active in the post-transplant setting. When brentuximab vedotin was administered in a weekly dosing schedule, early complete responses (CRs) were observed. The PET scan is highly predictive of post-transplant outcome.

Brentuximab vedotin has 2 published dosing schedules. The US Food and Drug Administration (FDA) approved dosing of once every 3 weeks. A phase 1 trial that examined weekly dosing determined the dose to be 1.2 mg/kg, with patients receiving treatment 3 weeks on and 1 week off.³ Overall, the results were at least as good as treatment administered once every 3 weeks (Table 1). The majority of patients who achieved a CR achieved it within the first restaging. This regimen was considered a good one to try to induce CRs quickly to get patients to transplant.

In this study, patients received 2 cycles of weekly brentuximab vedotin, and then they were reevaluated by PET.⁴ Those with normalized PET scans went right to transplant. PET scans with a Deauville score of 1 or 2 were considered negative. Patients with persistent abnormalities received 2 cycles of augmented

	0.4 mg/kg (n=4)	0.6 mg/kg (n=4)	0.8 mg/kg (n=6)	1.0 mg/kg (n=10)	1.2 mg/kg (n=12)	1.4 mg/kg (n=5)	Total (N=41)
ORR, n (%)	0	2 (50)	4 (67)	7 (70)	7 (58)	4 (80)	24 (59)
CR, n (%)	0	0	4 (67)	5 (50)	3 (25)	2 (40)	14 (34)
PR, n (%)	0	2 (50)	0	2 (20)	4 (33)	2 (40)	10 (24)
SD, n (%)	4 (100)	1 (25)	1 (17)	2 (20)	4 (33)	1 (20)	13 (32)
PD, n (%)	0	1 (25)	1 (17)	1 (10)	1 (8)	0	4 (10)

Table 1. Response Rates in a Phase 1 Study of Brentuximab Vedotin

CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Data from Fanale MA et al. Clin Cancer Res. 2012;18:248-255.3

ICE in which augmented ICE was double-dosed with bisphosphonates and etoposide, and then they were reevaluated by PET scan. Those whose PET scan was normalized went on to transplant, and those with persistent PET abnormalities were managed as per their treating physician.

The primary outcome for this study was rate of CR to the treatment program, assuming that some patients would receive only brentuximab vedotin. Basically, the treatment program was brentuximab vedotin plus or minus augmented ICE. The study used the Simon 2-stage design, with the assumption that a 60% rate of PET normalization would be clinically meaningful. This assumption was based on past observations. These criteria meant that 18 patients were needed in the first stage with 8 CRs. Then, an additional 28 patients were needed for a total planned enrollment of 46 patients, with 23 CRs required.

Among the first 33 patients who were enrolled and were evaluable for a response, the majority (70%) were male. Most patients had advanced-stage disease at enrollment, and 80% developed either primary refractory disease or relapsed within a year of their initial treatment. Extranodal sites of disease were present in 42% of the patients. Overall, this population was poor risk.

The study opened in January 2012 and had enrolled 40 patients at the time of this report, with the first 33 being evaluable for response. Normalization of PET scans occurred for 10 patients following just brentuximab vedotin, so these patients went on to transplant. Among the 23 patients who went on to receive augmented ICE, 16 had normalization of their PET scans and went on to transplant. An additional 7 patients had some areas of persistent abnormalities. Overall, although 7 patients had some persistent abnormalities, 32 of the 33 patients ultimately went on to transplant.

For the patients who received brentuximab vedotin, 10 of them had

ABSTRACT SUMMARY Two-Year Follow-Up of Patients With Relapsed/ Refractory Hodgkin Treated With Brentuximab Vedotin Prior To Reduced Intensity Allogeneic Hematopoietic Cell Transplantation

After autologous stem cell transplant, 50% of HL patients will relapse, and the median overall survival (OS) is only 2.4 years after the procedure. This retrospective analysis examined consecutive HL patients who received brentuximab vedotin and went on to receive a reduced-intensity allotransplant (abstract 140). Among the 36 patients who fit the inclusion criteria, 19 eventually went on to receive a transplant. Their median age was 31 years. The median number of prior therapies was 5, and 10 patients had received prior radiation. A prior allotransplant had been received by 18 of the 19 patients. The patients had a median of 8 cycles of brentuximab vedotin. At the time of transplant, 37% were in CR and 37% were PR. Transplants were match-related for 7 patients, match-unrelated for 9, and haploidentical for 3. After a median follow-up of 25.6 months, the 2-year OS was 79.3%, and the 2-year PFS was 59.3%. The 2-year relapse rate was 22.2%, and the 2-year nonrelapse mortality was 12.5%. Among patients in CR at transplant, the 2-year PFS was 71.4%, whereas it was 54.6% for patients not in CR at transplant (difference not significant). The median numbers of days to reach white blood cell engraftment and to reach platelet engraftment were both 14. The incidence of acute GVHD was 26.3%, whereas the chronic GVHD incidence was 73.7%. Brentuximab vedotin added prior to allotransplant did not adversely affect engraftment, GVHD, or survival. Further, brentuximab vedotin may provide sufficient disease control for selected patients to proceed to a reduced-intensity allotransplant.

normalization of their PET scans, with 4 of them having a Deauville score of 1 and 6 having a score of 2. The majority of the patients had a Deauville score of 4, although a split occurred among them and some of those patients did seem to have a very good response. Those responses were being examined further.

For the patients who went on to receive augmented ICE, the Deauville scores were notable in that no patients progressed between treatment with brentuximab vedotin and augmented ICE. Another 16 patients had normal PET scans, whereas 7 patients had some persistent abnormalities.

Overall, 79% of the patients achieved a CR following this treatment program, and all have gone on to transplant. Of the 7 patients who did not achieve a CR, the treating physician of 1 patient whose Deauville score was 3 decided to proceed to transplant, and that patient was doing fine. Further, 5 of the 7 patients were radiation-naive and had nodal-based disease, so they received radiation therapy and achieved either CR or near CR and went on to transplant. One patient had persistent disease and is currently under active therapy.

The most common adverse events (AEs) in patients receiving brentuximab vedotin were neuropathy (45%; all grade 1 or 2) and rash (70%; majority was grade 1 or 2). Some patients had significant pruritus and swelling of their hands, and received systemic steroids to help resolve the rash. Overall, this AE did not delay any treatment. One patient died; he had developed progressive multifocal leukoencephalopathy approximately 5 months after his allotransplant. He had primary refractory HL and had gone on to receive brentuximab vedotin, then 2 cycles of augmented ICE, and then a total lymphoid irradiation-based transplant. After 5 months, he developed progressive multifocal leukoencephalopathy. Notably, at that time, he had a CD4 percentage of approximately 14%, although he was negative for the human

immunodeficiency virus (HIV). His death occurred 2 months later.

In summary, this PET-adapted sequential therapy had a 79% CR rate, and 30% of the patients avoided ICE altogether. Five additional patients had a Deauville score of 3 and potentially would have achieved a score of 2, thus requiring ICE therapy, if they had received another cycle of treatment. A planned amendment to the study would give 3 cycles of brentuximab vedotin prior to reevaluation. Overall, although some patients were considered to have failed treatment because their PET scans had persistent abnormalities, all but 1 of them went on to transplant in either CR or near CR.

References

 Moskowitz AJ, Yahalom J, Kewalramani T, et al. Pretransplantation functional imaging predicts outcome following autologous stem cell transplantation for relapsed and refractory Hodgkin lymphoma. *Blood.* 2010;116:4934-4937. 2. Moskowitz CH, Matasar MJ, Zelenetz AD, et al. Normalization of pre-ASCT, FDG-PET imaging with second-line, non-cross-resistant, chemotherapy programs improves event-free survival in patients with Hodgkin lymphoma. *Blood.* 2012;119:1665-1670.

 Fanale MA, Forero-Torres A, Rosenblatt JD, et al. A phase I weekly dosing study of brentuximab vedotin in patients with relapsed/refractory CD30-positive hematologic malignancies. *Clin Cancer Res.* 2012;18:248-255.
Moskowitz AJ, Schoder H, Gerecitano J, et al. PETadapted sequential therapy with brentuximab vedotin and augmented-ICE induces FDG-PET normalization in 92% of patients with relapsed and refractory Hodgkin lymphoma [abstract 141]. *Hematol Oncol.* 2013;31(suppl 1).

Interim Results From a Phase II Study of PI3K-Delta Inhibitor Idelalisib in Patients With Relapsed Indolent Non-Hodgkin Lymphoma Refractory to Both Rituximab and an Alkylating Agent

✓ his phase 2 study addressed the activity of an inhibitor of the PI3-kinase (PI3K) δ in relapsed indolent double-refractory patients with NHL.¹ PI3Kδ is a kinase that is involved in the signal transduction of many cell surface receptors, including the B-cell receptor, some cytokine and chemokine receptors, and integrins. The PI3K p110 & isoform is largely expressed in lymphocytes. The signal is transferred downstream to elements that increase survival proliferation, motility, and homing. Fully inhibiting this pathway could be critical for B cells.

An oral inhibitor of PI3K δ has been developed, which was formerly called *CAL-101*, then *GS-1101*, and now *idelalisib*. In vitro, idelalisib can inhibit proliferation and induce apoptosis of many B-cell malignancies, both in cell lines and in ex vivo cells.² Also, idelalisib inhibits the homing and retention of malignant B cells in lymphoid tissue. This inhibitor is very specific for the δ isoform of PI3K, and it has little or no activity on the other isoforms of PI3K. Additionally, idelalisib has shown promising results in relapsed/refractory chronic lymphocytic lymphoma (CLL) and in relapsed/refractory indolent HL.³⁻⁷

Patients with indolent NHL who have already received alkylating agents and rituximab are a population that has been poorly studied to date. These patients have few treatment options. Although there are not many reports of these patients, they clearly have a high unmet medical need for new therapies. A phase 1/2 clinical trial of ofatumumab in rituximab-refractory patients, two-thirds of whom were chemorefractory, had a response rate of 50% in 1 cohort.8 Bendamustine was developed in rituximab-refractory patients, although only 1 subset of these patients was chemorefractory.9 No comparative data exist for the population examined in this study.

This phase 2 trial studied a singleagent monotherapy in refractory, indolent NHL. Patients received idelalisib 150 mg orally twice a day continuously, until progression or drop-out. Tumors were assessed at study entry and then every 8 weeks until week 36. Thereafter, tumors were assessed at week 48, and then every 12 weeks. The computed tomography (CT) scans were evaluated by an independent working committee with 2 radiologists, and the evaluation also included clinical review. The primary endpoint of this study was overall response rate (ORR) with classical secondary endpoints.

The key eligibility criteria for these patients were previously treated indolent NHL, including small lymphocytic lymphoma (SLL), follicular lymphoma (FL), marginal zone lymphoma (MZL), and lymphoplasmacytic lymphoma/ Waldenström macroglobulinemia (LPL/ WM). The patients' Eastern Cooperative Oncology Group (ECOG) scores were 0 to 2. Indolent NHL was defined as refractory to rituximab and an alkylating agent, meaning a lack of response while on therapy or progression after therapy within 6 months of completion of therapy, which had to be documented by imaging. Patients had to have measurable disease. Patients with anemia or neutropenia could not be recruited to the study.

The enrolled patient population had a slight predominance of men (64%), and the median age was 64 years (range, 33-87 years). A majority of the patients had FL (n=72; 58%), and 28 had SLL, 15 had MZL, and 10 had LPL/WM. A few patients had minor neutropenia, anemia, and



Figure 1. Progression-free survival (PFS) in an interim analysis of Study 101-09, a phase II study of idelalisib in patients with relapsed indolent non-Hodgkin lymphoma refractory to both rituximab and an alkylating agent. Adapted from Salles GA et al. *Hematol Oncol.* 2013;31(suppl 1): Abstract 064 bis.¹

thrombocytopenia at study entry. One-third of the patients had elevated lactate dehydrogenase at study entry, and a quarter had at least 1 lesion that was larger than 7 cm.

The median number of prior treatment regimens for this patient cohort was 4 (range, 2-12). All the patients had received rituximab. Approximately two-thirds of the patients had received bendamustine, two-thirds had received an anthracycline, and one-third had received a purine analogue. The median time that patients received their last regimen prior to study entry was 4.2 months.

Among the patients who had received rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), 77% were refractory. Among patients who had received bendamustine and rituximab, 72% were refractory. Among patients who received rituximab, cyclophosphamide, vincristine, and prednisone (R-CVD), 75% were refractory. Approximately half of the patients who had received bendamustine were refractory to it. A total of 79% of the patients were refractory to at least 2 regimens, and three-quarters were refractory to their last regimen.

As of the cutoff date in February 2013, based on the last patient who had

ABSTRACT SUMMARY CALGB 50803 (ALLIANCE): A Phase 2 Trial of Lenalidomide Plus Rituximab in Patients With Previously Untreated Follicular Lymphoma

This multicenter phase 2 trial enrolled 66 patients with untreated FL (abstract 063). The patients received lenalidomide on 28-day cycles plus rituximab. The patients were a median age of 53 years, 49% were male, and 31% had a FLIPI score below 2. AEs of grade 3 or 4 that occurred in more than 5% of the patients included neutropenia (20%), lymphopenia (8%), rash (8%), fatigue (6%), and leukopenia (5%). Grade 2 or higher AEs that affected more than 5% of patients included fatigue (25%), infusion reaction (17%), upper respiratory reaction (13%), nausea (8%), constipation (7%), increased alanine aminotransferase (7%), hyperglycemia (7%), hypophosphatemia (7%), pain (6%), oral mucositis (5%), and myalgia (5%). One patient experienced febrile neutropenia (2%). A total of 51 patients completed 12 cycles of lenalidomide (81%). Early termination occurred because of AEs in 6 patients and because of treatment refusal in 5 patients. Among the 54 evaluable patients, the response rate was 93%, including 72% CRs and 20% PRs. Stable disease occurred in 2 patients (3.7%), and 2 did not respond (3.7%). The 2 nonresponders stopped treatment early because of AEs. After a median follow-up of 1.3 years, 6 patients had progressed. Overall, the combination of lenalidomide plus rituximab was well tolerated in patients with untreated FL. The planned therapy was completed by the majority of the patients. The ORR and CR were comparable with published chemotherapycontaining regimens. PFS will be evaluated in longer follow-up.

enrolled and completed 16 weeks of treatment, approximately half (48%) of the patients were still receiving therapy, whereas 52% of the patients discontinued treatment owing to disease progression, AEs, or investigator request. These discontinued patients included 4 who proceeded to stem cell transplant, 1 who died from cardiac arrest, 1 patient with pneumonia, 1 patient with sepsis, 1 patient with progressive disease, and 2 patients who withdrew consent. The patients were exposed to idelalisib for a mean of 6.6 months and a median of 5.6 months. Some patients who were still under study had received 19 months of drug exposure.

The ORR was 53.4%, with 67% of the patients responding to the agent based on strict evaluation. The CR rate was a low 4%, and the majority of responses were PRs. A minor response occurred in 2 patients with LPL/WM, as defined by the International Workshop on Waldenström's Macroglobulinemia.¹⁰

More than one-third of the patients had SD. Only 10% of the patients progressed. Two patients were not evaluated. Interestingly, patients responded rapidly; the median time to the first response was approximately 2 months.

Criteria associated with ORR were examined, including refractoriness to last therapy, number of prior therapies, prior bendamustine use, different histologies, bulk of the disease, and age. All the patients responded at a rate close to 50%, although those with LPL/WM had a lower response rate. Otherwise, the response rate did not differ according to the different criteria, including patients who were or were not refractory to their last therapy and patients with or without bulky disease.

The duration of response was very close to 1 year, indicating that some patients maintained the benefit of response. Some patients were only evaluated once or twice during this time. More follow-up is needed to consolidate the data. The current median progressionfree survival (PFS) was 11.4 months, which is very encouraging for a difficult population (Figure 1). Again, these data require more follow-up.

One of the most common AEs was grade 3 or higher diarrhea, which occurred in 10% of patients. Fatigue was noted in 28 patients, with 2 patients at grade 3 or above.

Serious AEs or AEs leading to discontinuation included pyrexia, pneumonia, diarrhea, dehydration, febrile neutropenia, colitis, and acute renal failure. Approximately half of the patients had an elevation of transaminases (48%), but only 13% had a grade 3 or higher transaminase elevation. A postprotocol update regarding transaminases interrupted the drug and rechallenged the patient. Out of 16 patients who experienced these transaminase events, 14 were rechallenged, and a majority of them (n=11) successfully took the drug again for some time.

In summary, idelalisib was active in highly refractory patients with indolent NHL. The ORR was 54%. The responses were durable. These encouraging data must be consolidated over time. The current duration of response was 12 months, and the PFS was 11.5 months. The safety profile was manageable. This compound presents an interesting option in these indications for patients with a high unmet therapeutic need. Also, this drug may be worth pursuing for use in other situations for patients with indolent malignancies.

References

 Salles GA, Kahl BS, de Vos S, et al. Interim results from a phase II study of PI3Kdelta inhibitor idelalisib in patients with relapsed indolent non-Hodgkin lymphoma refractory to both rituximab and an alkylating agent [abstract 064 bis]. *Hematol Oncol.* 2013;31(suppl 1).
Hoellenriegel J, Meadows SA, Sivina M, et al. The phosphoinositide 3'-kinase delta inhibitor, CAL-101, inhibits B-cell receptor signaling and chemokine networks in chronic lymphocytic leukemia. *Blood.* 2011;118:3603-3612.
Barrientos JC, Furman RR, Leonard J, et al. Update on a phase I study of the selective PI3Kô inhibitor idelalisib (GS-1101) in combination with rituximab and/ or bendamustine in patients with relapsed or refractory CLL [abstract 7017]. *J Clin Oncol.* 2013;31(suppl 15).

ABSTRACT SUMMARY ECHELON-2: Phase III Trial of Brentuximab Vedotin and CHP Versus CHOP in the Frontline Treatment of Patients with CD30+ Mature T-Cell Lymphomas

Mature T-cell lymphomas, which include sALCL, are aggressive neoplasms with 5-year OS rates that range from 12% to 49%, depending on the histologic subtype. Response rates for anthracycline-based multiagent chemotherapy regimens have ranged from 76% to 88%. Brentuximab vedotin has shown efficacy in a phase 2 study as a single agent in relapsed sALCL. Evidence of clinical activity of brentuximab vedotin in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) was observed in a phase 1 study in the frontline treatment of mature T-cell lymphomas, including sALCL (Fanale MA et al. Presented at: 54th ASH Annual Meeting; abstract 60). This phase 3 trial in frontline treatment of CD30-positive mature T-cell lymphoma is randomized, double-blind, placebo-controlled, and multicenter. It will evaluate the safety and efficacy of 1.8 mg/kg brentuximab vedotin with CHP vs CHOP. This global trial, whose enrollment began early in 2013, requires eligible patients to have FDG-avid disease, as determined by PET, and measurable disease of at least 1.5 cm by CT. The trial will randomize approximately 300 patients 1:1 to receive brentuximab vedotin plus CHP or CHOP every 3 weeks for 6 to 8 cycles. The randomization will be stratified by those who are sALCL positive for anaplastic lymphoma kinase vs other histologic subtypes and by IPI score (0-1, 2-3, or 4-5). The trial has a target of 75% of the enrolled patients having sALCL. The primary objective is to compare PFS between the 2 treatment arms. An independent review facility will determine PFS. Secondary objectives include comparing PFS per independent review in sALCL patients, safety, OS, and the complete remission rate between the 2 study arms. Once patients complete treatment, they will be followed for disease progression, medical resource utilization, quality of life, and survival. After treatment, stem cell transplant is permitted. Assessments of efficacy will use the Revised Response Criteria for Malignant Lymphoma (Cheson BD et al. J Clin Oncol. 2007;25:579-586). Patients will receive CT and PET scans at baseline, after cycle 4, and after completing treatment. During follow-up, CT scans will occur at regular intervals until disease progression, death, or analysis of the primary endpoint. Patient safety will be assessed throughout the study until 30 days after the last dose of the study treatment.

4. Benson DM, Kahl BS, Furman RR, et al. Final results of a phase I study of idelalisib, a selective inhibitor of PI3Kô, in patients with relapsed or refractory indolent non-Hodgkin lymphoma (iNHL) [abstract 8526]. *J Clin Oncol.* 2013;31(suppl 15).

5. Brown JR, Furman RR, Flinn I, et al. Final results of a phase I study of idelalisib (GSE1101) a selective inhibitor of PI3Kô, in patients with relapsed or refractory CLL [abstract 7003]. *J Clin Oncol.* 2013;31(suppl 15).

6. Leonard J, Wagner-Johnston ND, Coutre SE, et al. Tolerability and activity of combinations of the PI3K8 inhibitor idealisib (GS-1101) with rituximab and/or bendamustine in patients with previously treated, indolent non-Hodgkin lymphoma (iNHL): updated results from a phase I study [abstract 8500]. J Clin Oncol. 2013;31(suppl 15).

7. Spurgeon SEF, Wagner-Johnston ND, Furman RR, et al. Final results of a phase I study of idelalisib, a selective inhibitor of phosphatidylinositol 3-kinase

P1106 (PI3K\delta), in patients with relapsed or refractory mantle cell lymphoma (MCL) [abstract 8519]. *J Clin Oncol.* 2013;31(suppl 15).

8. Coiffier B, Lepretre S, Pedersen LM, et al. Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a phase 1-2 study. *Blood.* 2008;111:1094-1100.

9. Cheson BD, Friedberg JW, Kahl BS, Van der Jagt RH, Tremmel L. Bendamustine produces durable responses with an acceptable safety profile in patients with rituximab-refractory indolent non-Hodgkin lymphoma. *Clin Lymphoma Myeloma Leuk.* 2010;10:452-457.

 Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological definition of Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. *Semin Oncol.* 2003;30:110-115. Progression-Free Survival Analyses of Two Pivotal Phase 2 Studies of Brentuximab Vedotin in Patients With Relapsed or Refractory Hodgkin Lymphoma or Systemic Anaplastic Large-Cell Lymphoma

G035-0003^{1,2} and SG035-0004^{3,4} were pivotal, single-arm phase 2 trials demonstrating that brentuximab vedotin (administered at 1.8 mg/kg intravenously every 21 days for up to 16 cycles) had a manageable safety profile and antitumor activity in patients with relapsed/refractory HL following ASCT (SG035-0003) and relapsed/ refractory systemic anaplastic large cell lymphoma (sALCL; SG035-0004). A post-hoc analysis of data from these studies compared rates of PFS achieved with brentuximab vedotin to those achieved with the patients' last prior systemic therapy.5 The analysis found that brentuximab vedotin was associated with a longer PFS in more than 60% of these heavily pretreated patients. In addition, PFS achieved with the last prior systemic therapy was not predictive of PFS achieved with brentuximab vedotin, suggesting lack of cross-resistance to brentuximab vedotin therapy.

In the SG035-0003 study, patients with relapsed/refractory HL post-ASCT received a median of 3.5 systemic chemotherapy regimens (range, 1-13), not including ASCT, before enrollment. Most patients (91%) received doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) as frontline therapy. Approximately one-half of patients received ICE, the most common second-line therapy. In the SG035-0004 study, patients with relapsed/refractory sALCL had received a median of 2 prior chemotherapy regimens (range, 1-6), not including ASCT, before enrollment. The most common treatment was CHOP, which was given as first-line induction therapy and maintenance therapy. Combination regimens were more frequent than monotherapy. As seen with the pat-



Figure 2. In an analysis of PFS in 2 pivotal phase 2 studies of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma or systemic anaplastic large-cell lymphoma, median PFS was 9.3 months with brentuximab vedotin vs 6.1 months with last prior systemic therapy. PFS, progression-free survival. Adapted from Radford J et al. *Hematol Oncol.* 2013;31(suppl 1): Abstract 303.⁵

terns with relapsed/refractory HL post-ASCT, there was no apparent pattern for third-line therapy in these patients with relapsed/refractory sALCL.

Among the 102 relapsed/refractory HL patients, the median age was 31 years (range, 15-77 years), and 47% were male. The 58 relapsed/refractory sALCL patients were older, with a median age of 52 years (range, 14-76 years); 57% were male. The median number of prior chemotherapy regimens was 3.5 in the relapsed/refractory HL group and 2 in the relapsed/refractory sALCL group. In both studies, investigators assessed PFS in the intent-to-treat (ITT) population. Data were also gathered regarding prior systemic treatment histories and post-brentuximab vedotin stem cell transplant (SCT) experience by at least 2 independent reviewers.

At the data cut (median follow-up of 27 months), 62% of patients with relapsed/refractory HL post-ASCT had achieved a longer PFS with brentuximab vedotin than with their last prior systemic therapy. Median PFS was 9.3 months with brentuximab vedotin vs 6.1 months with the last prior systemic therapy (Figure 2). A longer PFS with brentuximab vedotin than with the last prior systemic therapy was found in 63% of patients who relapsed within 6 months of their most recent ASCT and 65% of patients who relapsed within 12 months of their most recent ASCT (Table 2). Among the patients with relapsed/refractory sALCL, 67% had achieved a longer PFS with brentuximab vedotin than with their last prior systemic therapy at the data cut (median follow-up of 22 months). The median PFS was 19.6 months with brentuximab vedotin and 5.9 months with the last prior systemic therapy.

Stem cell transplant after brentuximab vedotin was more common among patients with relapsed/refractory sALCL than among patients with relapsed/refractory HL. In the

	-			
	PFS With Brentuximab Vedotin	PFS With Last Prior Therapy		
Parameter	ITT Population (N=102)			
Median PFS, months (range)	9.3 (1.2+ to 36.4)	6.1 (1.0-110.2)		
Improved PFS with brentuximab vedotin vs last prior systemic therapy, n (%)	63 (62)			
	Relapsed <8 Months After Last ASCT (n=46)			
Median PFS, months (range)	9.3 (1.2+ to 35.3+)	5.9 (1.1-12.0)		
Improved PFS with brentuximab vedotin vs last prior systemic therapy, n (%)	29 (53)			
	Relapsed <12 Months After Last ASCT (n=72)			
Median PFS, months (range)	8.4 (1.2+ to 36.4)	5.1 (1.0-35.5)		
Improved PFS with brentuximab vedotin vs last prior systemic therapy, n (%)	47 (65)			

Table 2. PFS Achieved With Brentuxim	b Vedotin and Last Prior S	ystemic Therapy
--------------------------------------	----------------------------	-----------------

ASCT, autologous stem cell transplant; ITT, intent to treat; PFS, progression-free survival. Data from Radford J et al. Hematol Oncol. 2013;31(suppl 1): Abstract 303.

SG035-0004 trial, 20 patients underwent SCT after receiving brentuximab vedotin (ASCT in 9, and allogeneic SCT in 11). Seventeen patients underwent a transplant after treatment with brentuximab vedotin alone. Other patients first received brentuximab vedotin followed by dexamethasone, rituximab, oxaliplatin, and cytarabine (R-DHAOX; n=1), brentuximab vedotin followed by belinostat followed by pralatrexate (n=1), and liposomal doxorubicin followed by dexamethasone (n=1). In the SG035-0003 study, 20 patients underwent SCT after receiving brentuximab vedotin (ASCT, n=1; allogeneic SCT, n=18; ASCT followed by allogeneic SCT, n=1). Seven of these patients underwent a transplant after treatment with brentuximab vedotin alone.

In both groups, the most common treatment-emergent AE was peripheral neuropathy. Among patients with relapsed/refractory HL, the most common (\geq 20%) treatment-emergent AEs of all grades were peripheral sensory neuropathy (47%), fatigue (46%), nausea (42%), upper respiratory tract infection (37%), diarrhea (36%), pyrexia (29%), neutropenia (22%), vomiting (22%), and cough (21%). The most common grade 3/4 AEs (\geq 5%) were neutropenia (14%/6%) and peripheral sensory neuropathy (9%/none). Other grade 3 or higher AEs occurring in at least 5% of patients were thrombocytopenia (8%) and anemia (6%).

Among patients with relapsed/ refractory sALCL, the most common all-grade treatment-emergent AEs ($\geq 20\%$) were peripheral neuropathy (57%), nausea (40%), fatigue (38%), pyrexia (34%), diarrhea (29%), rash (24%), constipation (22%), and neutropenia (21%). Grade 3/4 AEs occurring in at least 5% of patients were peripheral neuropathy (17%/none) and neutropenia (12%/9%). Other grade 3 or higher AEs occurring in at least 5% of patients were thrombocytopenia (14%) and anemia (7%).

References

1. Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol.* 2012;30(18):2183-2189.

2. Chen RW, Gopal AK, Smith SE, et al. Long-term survival analyses of an ongoing phase 2 study of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma [abstract 3689]. *Blood.* 2012;120(21).

 Pro B, Advani R, Brice P, Bartlett NL, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J Clin Oncol.* 2012;30(18):2190-2196.
Pro B, Advani RH, Brice P, et al. Long-term remissions observed in an ongoing phase 2 study of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma [abstract 2745]. *Blood.* 2012;120(21).

5. Radford J, Younes A, Pro B, et al. Progression-free survival analyses of two pivotal phase 2 studies of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma or systemic anaplastic large-cell lymphoma [abstract 303]. *Hematol Oncol.* 2013;31(suppl 1).

A Phase II Trial of Response-Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging: U.S. Intergroup S0816

reliminary results of a phase 2 US Intergroup study of responseadapted therapy for HL at stage 3 to 4 using early interim 18F-fluorodeoxyglucose-enhanced (FDG) PET imaging were presented.1 This study was based on the acknowledgment that doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) remains the standard of care for advanced HL at this time in the United States. ABVD is believed to cure approximately 70% of the patients treated, which is an unsatisfactory cure rate. Although escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) might cure more patients, it is more toxic and causes infertility.2

Reports suggest that interim PET/ CT scans after 2 cycles of ABVD are highly predictive of treatment failure with ABVD.³ Patients who were PETpositive after 2 cycles of ABVD have a chance of achieving PFS of 10% to 15%, compared with perhaps 90% if they are PET-negative. This finding suggested an opportunity for early dose escalation in PET-positive patients to try to improve their outcomes, while sparing the majority of patients who do not need escalated therapy. This approach led to the design of this trial.

The trial had 2 parallel treatment cohorts, HIV-negative and HIV-positive, which were analyzed separately. All the patients began with 2 cycles of ABVD and then underwent FDG-PET imaging. The scans were electronically transmitted to the Cancer and Leukemia Group B (CALGB) Imaging Center for central review. The patients who were PET2-negative received all 4 cycles of ABVD, whereas those who were PET2-positive received either escalated-dose BEACOPP for 6 cycles if they were HIV-negative or BEACOPP baseline for 6 cycles if they were HIV-positive.

The study had 2 co-primary objectives. The first was to improve the 2-year PFS of the HIV-negative patients from the historic value of 70% to 78% with response-adapted therapy, which would require 278 patients in order to detect this difference with 89% power. The second was to improve the 2-year PFS of the adverse PET2-positive subgroup from the historic value of approximately 15% to 30%, to 48% with responseadapted therapy. Approximately 60 PET2-positive patients were required in order to detect this difference with 87% power.

The trial had several secondary objectives. First, it sought to document the feasibility of performing such a centralized FDG/PET review in the US cooperative group setting, which had never been done before. The study also sought to estimate ORR, CR, 2-year PFS, and overall survival for the HIV-negative and HIV-positive subsets. The study also sought to evaluate the toxicity of such response-adapted therapy, to explore serum and tissue biomarkers that might be associated with outcomes, and to follow the viral loads and CD4 counts in patients who were HIV-positive.

Patients were eligible for this trial if they had stage 3 or 4 classical HL, as confirmed by centralized review of a diagnostic biopsy material. Patients were ages 18 to 60 years. They had measurable disease, no prior therapy, a performance status of 0 to 2, and no other serious medical conditions. All patients underwent routine blood testing and bone marrow biopsy at baseline. If the results were positive, these tests were repeated after treatment was completed on day 197. Physical examinations occurred, and laboratory data were collected with each cycle of therapy and after therapy on day 197, day 276, day 365, and then every 6 months or whenever signs or symptoms of relapse occurred. Baseline hormone levels were analyzed and then followed once a year as a crude measure of fertility.

PET/CT imaging was performed on 3 occasions: at baseline, after cycle 2, and 6 to 8 weeks after therapy was completed. CT scans were done at baseline, when treatment ended, every 6 months in year 2, and then annually until year 5, or whenever symptoms and signs of relapse occurred. Treatment with ABVD was administered according to the standard dosage schedule. Physicians were instructed to give full doses on time, regardless of the blood counts, unless there was fever or infection. The baseline and escalated BEACOPP regimens were given as described by the German Hodgkin's Study Group.

The accrual rate was 10 to 20 patients per month during most months. The study enrolled 371 patients, including 358 who were HIV-negative and only 13 who were HIV-positive. Among the eligible 356 patients, 351 completed the planned treatment. The enrolled patients had a median age of 32 years. Most were male (57%) and white (80%). Nearly half (49%) had stage 4 disease, and 61% had B symptoms. Bulky disease of more than 10 cm in diameter was present in 18% of the patients. More than half (51%) had an adverse International Prognostic Score of 3 to 7, and 4% were HIV-positive.

Interim FDG-PET scans were interpreted based on Deauville scores. A score of 4 or 5 was considered positive for the interim scan after 2 cycles.



Figure 3. In a phase II trial of responseadapted therapy of stage III to IV Hodgkin lymphoma using early interim 18F-fluorodeoxyglucose-enhanced positron emission tomography imaging, patients who received continued ABVD had a CR rate of 96% and a PR rate of 4%. Among patients who received escalated BEACOPP, the CR rate was 49%, and the PR rate was 42%. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; CR, complete response; PR, partial response. Data from Press O et al. Hematol Oncol. 2013;31(suppl 1): Abstract 124.1

Although there was concern at the start of the study regarding whether reasonable turnaround times could be achieved in the cooperative group setting, they were achieved. The nuclearmedicine physicians turned 80% of the scans around in less than 2 days, and 95% in less than 4 days. Interim scans from 362 patients were sent for centralized review, and 296 (82%) were PET2-negative. All of these 296 patients went on to receive 4 cycles of ABVD for a total of 6 cycles. Positive PET2 scans occurred in 66 patients (18%), and they were escalated to BEACOPP, which was refused by 7. Although 59 registered for escalated

BEACOPP, only 54 patients ultimately received escalated BEACOPP based on physician or patient preference.

Among the patients who received continued ABVD, the CR rate was 96% and the PR rate was 4%. Among the patients who received escalated BEACOPP, the CR rate was 49% and the PR rate was 42% (Figure 3).

For HIV-negative patients, the preliminary overall survival was 95% at a median follow-up of approximately 1.5 years. A total of 9 deaths occurred, with 6 of them due to HL.

The estimated 2-year PFS was 76%, which is 2% lower than the protocol goal. This outcome will require further follow-up. When PFS was examined according to study arm, the PFS objective was easily met. The arm that was switched to escalated BEA-COPP, which would be estimated to have a 15% PFS, had a 61% 2-year PFS. For PET2-negative patients, the 2-year PFS was 79%.

As expected, the toxicity was greater in the patients who crossed over to BEACOPP. The patients in the BEACOPP arm experienced more grade 3 and 4 neutropenia and infection, along with much more thrombocytopenia, anemia, and febrile neutropenia. The study had 3 treatment-related deaths, which included 1 of 283 (0.4%) on ABVD due to bleomycin lung toxicity, and 2 of 50 (4%) on BEACOPP. The BEA-COPP deaths were due to sepsis (1 patient) and pneumonitis (1 patient).

Among the 13 HIV-positive patients enrolled, 11 were PET2negative, and they all received ABVD. Among the 2 PET2-positive, HIV-positive patients, 1 received BEACOPP as planned and 1 declined. The HIV- positive patients had 9 CRs and 2 PRs. Two patients were pending evaluation. The toxicities were manageable. No patients had died in the HIV-positive arm, and 12 of 13 were progressionfree at the time of this analysis.

In conclusion, response-adapted therapy with centralized, interim FDG-PET review is highly feasible in the US cooperative group setting. Early results suggest that PFS can be significantly improved in PET2-positive patients if they are switched over and escalated to a BEACOPP regimen, at least compared with the expected historical experience seen with continued ABVD. Ongoing phase 3 studies are comparing response-adapted therapy with interim PET scanning versus standard therapy. Additionally, molecular biomarker studies are under way that will involve a variety of serum and tissue biomarkers. It is hoped that these studies will provide some insight into patients who are PET2-negative but still progress, particularly concerning whether they will benefit from a switch to escalated-dose BEACOPP or other novel therapies. Further followup of this study is necessary.

References

1. Press O, LeBlanc M, Rimsza LM, et al. A phase II trial of response-adapted therapy of stage III-IV Hodgkin lymphoma using early interim FDG-PET imaging: U.S. Intergroup S0816 [abstract 124]. *Hematol Oncol.* 2013;31(suppl 1).

 Bauer K, Skoetz N, Monsef I, Engert A, Brillant C. Comparison of chemotherapy including escalated BEA-COPP versus chemotherapy including ABVD for patients with early unfavourable or advanced stage Hodgkin lymphoma. *Cochrane Database Syst Rev.* 2011:CD007941.

3. Gallamini A, Hutchings M, Rigacci L, et al. Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. J Clin Oncol. 2007;25:3746-3752.

Safety and Efficacy of Brentuximab Vedotin for the Treatment of Relapsed or Refractory Mature T-/NK-Cell Lymphomas

ature T-cell lymphoma includes diverse subtypes such as angioimmunoblastic T-cell lymphoma (AITL) and peripheral T-cell lymphoma not otherwise specified (PTCL-NOS). The expression of CD30 is variable except for anaplastic large cell lymphoma (ALCL). In general, patients with refractory disease or recurrent disease after the initial treatment have an extremely poor outcome. The overall survival curve for patients with T-cell lymphoma who experienced a recurrence or refractory disease after the initial treatment is very steep.1 These patients have limited options and need treatments that are effective and safe. Brentuximab vedotin has been extensively tested in HL and ALCL, which both have strong CD30 expression. In ALCL, the ORR was 86%, including a CR rate of 57% and CR duration of 13.2 months.² An ongoing phase 2 study is examining brentuximab vedotin for other NHLs positive for CD30. Oki and colleagues presented data on T-cell lymphomas.³

The study design required patients to have CD30-positive NHL. They could not have ALCL or primary cutaneous T-cell lymphoma. The CD30 expression was determined by immunohistochemistry by the local hematopathology laboratory. A central laboratory review also occurred, although it was not required at the time of enrollment. All patients received at least 1 systemic treatment prior to enrollment. The treatment was the standard use of brentuximab vedotin, which is 1.8 mg/kg intravenously every 3 weeks until progression of disease or unacceptable toxicity. Responses were evaluated after 2 cycles, after 4 cycles, and then at every 3 cycles thereafter. The disease response assessment was based on the revised response criteria.

The study's primary objective was to determine the ORR in this

patient population. Secondary objectives included assessing the correlation between CD30 expression and tumor shrinkage, PFS, and safety of the drug in this population.

At baseline, the enrolled patients included 11 with AITL and 18 with PTCL-NOS. Most patients were male, and the median age was 65. More than half of the patients had primary disease that was refractory to the frontline therapy, and more than half had disease that was refractory to the most recent systemic treatment. The median number of systemic therapies prior to study enrollment was 2.

When the best clinical response in this study was summarized, not all of the enrolled patients had been officially evaluated for their response, so the number of patients was smaller than the actual enrollment. In AITL, the ORR was 50%, including 40% CRs. In PTCL-NOS, the rate of ORR was 25%, with 17% achieving CR (Figure 4). Median duration of the objective response had not been reached by the time of the last data cutoff.

Many patients experienced tumor shrinkage, which was defined as the PET scan becoming negative. When the correlation between maximum tumor shrinkage and the frequency of the CD30 expression in the central laboratory was studied, no real correlation was observed. Some specimens showed CD30 expression by the local laboratory review but not the central laboratory review. Many patients had very low or no expression of CD30 and yet had clinically significant shrinkage of the tumor.

Treatment was still being received by 15 patients; 14 patients withdrew from the study because of disease progression. Progressive disease was reported in 7 patients, and 3 patients withdrew based on a lack of clinical benefit. Disease progression caused 2 patients to be taken off



Figure 4. In a study examining brentuximab vedotin for the treatment of relapsed or refractory mature T-lymphoma or natural killer–cell lymphoma, ORR was 50% in AITL patients and 25% in patients with PTCL-NOS. AITL, angioimmunoblastic T-cell lymphoma; ORR, overall response rate; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified. Data from Oki Y et al. *Hematol Oncol.* 2013;31(suppl 1): Abstract 152.³

the study, and AEs that included grade 3 neutropenia and pneumonitis led to 2 other patients being taken off the study. The median number of treatment cycles was 4 in adult T-cell lymphoma (ATCL) and 2 in PTCL-NOS. Approximately half of the patients were still receiving treatment at the day of data cutoff.

AEs that occurred in more than 10% of the enrolled patients, regardless of their association with the actual treatment, included fatigue, pyrexia, chills, decreased appetite, and peripheral neuropathy. Peripheral neuropathy seemed to be less frequent than in the previous pivotal studies, which may be due to the short duration of treatment in this study compared with the studies of HL and ATCL.^{2,4} Grade 3 or 4 AEs that were considered related to the study included grade 3 neutropenia in 3 patients. Other grade 3 AEs included decreased appetite, dyspnea, hypertension, hypoxia, peripheral motor neuropathy, and tumor lysis syndrome. One patient experienced a

grade 4 pulmonary edema. Within 30 days of the last dose, 3 patients died, all from disease progression.

An example of a patient with an impressive response to the treatment was a 62-year-old woman with AITL. She had been treated with 2 regimens prior to enrolling in the study. After study enrollment, she experienced rapid response with rapid tumor shrinkage. After 2 cycles, her PET scan became negative. She remained in CR after 1 year. She had recently received cycle 16 of treatment at the time of this report.

In summary, this study has shown promising antitumor activity of brentuximab vedotin in PTCL, particularly in ATCL. The ORR was 50%, including a CR rate of 40%. Preliminary results suggested that the responses were durable. Responses were seen regardless of CD30 expression. Interestingly, tumors with no CD30 expression also had a clinical response to the treatment. The data will continue to be updated and shared in the future.

References

 Mak V, Hamm J, Chhanabhai M, et al. Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. *J Clin Oncol.* 2013;31:1970-1976.
Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory sys-

ABSTRACT SUMMARY A Phase I Study of Bispecific CD30/CD16a TandAb Antibody AFM13 in Patients With Relapsed or Refractory Hodgkin Lymphoma

This open-label, single-arm, phase 1, dose-escalation study examined AFM13 in heavily pretreated patients with relapsed or refractory HL (abstract 042). The bispecific, tetravalent TandAb antibody AMF13 targets CD30 on HL tumor cells and recruits natural killer cells through CD16A. The design of this immunotherapy addresses deficiencies of antibodies, which have reduced binding to the 158F allotype of CD16A and also have nonselective binding to both CD16A and nonsignaling CD16B receptors on immune effector cells. The study examined 7 dose levels, ranging from 0.01 mg/kg to 7.0 mg/kg, in cohorts of 3 patients. A cycle of 4 weekly doses was received by each patient, and responders received a second cycle. The most common AEs were grade 1 or 2 infusion reactions. The dose levels were all well tolerated and safe. A clinical benefit was induced by AFM13 in 50% of the patients, with tumor volumes being reduced in a dose-dependent manner. Ex vivo study of the mode of action of AFM13 found a significant dose-dependent increase in activated natural killer cells and reduction in soluble CD30 levels. This finding indicated a correlation between antitumor activity and response biomarkers. Several patients had low level expression of CD30 on natural killer cells, which was not found to inhibit cytotoxicity mediated by natural killer cells. The half-life of AFM13 was 1 day, which is substantially increased compared with the alternative diabody-like formats currently being clinically investigated for hematologic malignancies. The biological activity of AFM13 is encouraging. AFM13 could potentially become a new targeted therapy for patients with heavily pretreated HL.

temic anaplastic large-cell lymphoma: results of a phase II study. *J Clin Oncol.* 2012;30:2190-2196. 3. Oki Y, Horwitz S, Bartlett NL, et al. Safety and efficacy of brentuximab vedotin for the treatment of relapsed or refractory mature T-/NK-cell lymphomas [abstract 152]. *Hematol Oncol.* 2013;31(suppl 1). 4. Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol.* 2012;30:2183-2189.

Phase I Study of the Anti-CD22 Antibody-Drug Conjugate DCDT2980S With or Without Rituximab in Patients With Relapsed or Refractory B-Cell Non-Hodgkin's Lymphoma

he novel agent DCDT2980S is an anti-CD22 monoclonal antibody conjugated to monomethyl auristatin E (MMAE) via a protease-cleavable peptide linker (Figure 5). The peptide linker is rapidly internalized upon binding. More than 95% of B-cell hematologic malignancies express CD22. MMAE is a potent microtubuledestroying agent. This antibody-drug

conjugate (ADC) has shown potent anti-tumor activity in murine xenograft models with B-cell lymphoma.¹

Advani and coworkers presented results from a phase 1 trial.² The key eligibility criteria was diagnosis of any relapsed or refractory B-cell lymphoma for which there was no corrective standard therapy.² Patients had to have measurable disease, adequate lymphatic and renal function, and adequate hematologic function. The key exclusion criteria were previous allogeneic transplant, central nervous system lymphoma, or peripheral neuropathy that was higher than grade 1.

The study design started with a dose escalation of various cohorts to define the maximum tolerated dose (MTD). Then, the study had a single-



Figure 5. DCDT2980S is an anti-CD22 monoclonal antibody conjugated to monomethyl auristatin E via a protease-cleavable peptide linker.

agent expansion in patients with indolent non-Hodgkin lymphoma (NHL) or relapsed or refractory diffuse large B-cell lymphoma (DLBCL). The phase 1B part of this study combined DCDT2980S with rituximab.

This trial enrolled 65 patients, who had a median age of 65 years. Most of the patients had a performance status between 0 and 1. The median number of prior therapies was 3 (range, 1-11). All the patients had received prior rituximab. Approximately 10% had undergone a prior autologous transplant. Among the patients, 60% had relapsed or refractory DLBCL, 30% had FL, a minority had mantle cell lymphoma (MCL) and SLL, and 1 patient had gray zone lymphoma.

The treatment was fairly well tolerated. The predominant grade 3 or 4 AE was neutropenia, which occurred in 10% of the patients. Other AEs included peripheral neuropathy in a minority of patients and hyperglycemia.

The median number of cycles delivered was 4 as a single agent and 6 when delivered in combination with rituximab. Treatment was discontinued in approximately 20% of the patients, 18% needed a dose reduction, and 35% experienced treatment delays. Dr Advani noted that multiple delays in an individual patient were counted as separate events.

The treatment was discontinued in 20% of the patients mainly owing to peripheral neuropathy, which occurred in 9 patients. Other reasons for discontinuation included fever, femur fracture, atrial fibrillation, metastatic renal cancer, and myeloid maturation arrest. Dose reductions were also primarily caused by peripheral neuropathy. Treatment delays were due to fatigue, thrombocytopenia, and a variety of other causes without a clear pattern. Within 30 days of the last study dose, 2 patients died, and their deaths were considered unrelated to the treatment.

At baseline, 32% of patients had a history of peripheral neuropathy. The patients had all been treated with vincristine or a similar medication previously. Upon enrollment, 28% of patients had ongoing grade 1 peripheral neuropathy.

Considering those starting points, half of the patients reported grade 1 or 2 peripheral neuropathy, whether they received DCDT2980S alone or in combination with rituximab. Grade 3 or 4 peripheral neuropathy was reported in 8% for the single agent and 19% for the combination. Approximately half of the patients reported a worsening of peripheral neuropathy, meaning they went from grade 1 to 2, or from grade 2 to a higher grade. A complete reversal of peripheral neuropathy occurred with approximately 30% of the patients, whether they received the drug alone or in combination with rituximab.

DCDT2980S has a serum concentration profile that is similar between the total ADC and the antibody conjugate. The steady state was reached within 2 cycles. Preliminary analysis suggested that the combination did not have any effect on pharmacokinetics or the ADC-related analysis. The level of free MMAE was very low during the 21-day cycle.

The objective response rate was 40% with the single agent and 33% with the combination. The complete response (CR) rate was 16%. Partial

responses (PRs) occurred in 23% of the patients. Approximately 30% of the patients had stable disease (SD) with the single agent. For the combination with rituximab, 13% of patients had a CR, 20% had a PR, and 33% had SD.

In conclusion, DCDT2980S had an acceptable safety profile, as most of the AEs were grade 1 or 2. Neutropenia was the most frequent grade 3 or 4 AE. The peripheral neuropathy that patients experienced was manageable with dose delays or reductions. Some patients had to discontinue treatment. The MTD determined for single-agent therapy showed no compounding toxicity when combined with rituximab. The pharmacokinetic profile was acceptable, with mean peak plasma-free levels of MMAE that were more than 100-fold lower than the antibody-conjugated MMAE. The combination with rituximab had no impact on pharmacokinetics. Antitumor activity occurred in both DLBCL and FL in this heavily pretreated population with relapsed or refractory lymphoma. These responses were durable. Data at the time of this report were insufficient to determine if rituximab had an additive effect. The results support additional clinical evaluation in B-cell malignancies, and further research is under way.

References

1. Li D, Poon KA, Yu SF, et al. DCDT2980S, an anti-CD22-monomethyl auristatin E antibody-drug conjugate, is a potential treatment for non-Hodgkin lymphoma. *Mol Cancer Ther.* 2013;12:1255-1265. 2. Advani R, Chen A, Lebovic D, et al. Phase I study of the anti-CD22 antibody-drug conjugate (ADC) DCDT2980s with or without rituximab in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma [abstract 039]. *Hematol Oncol.* 2013;31(suppl 1).

Single-Agent Ibrutinib (PCI-32765) Is Highly Effective in Chronic Lymphocytic Leukemia (CLL) Patients With 17p Deletion

Tbrutinib has demonstrated activity in patients with high-risk chronic lymphocytic leukemia (CLL),¹ and a phase II clinical trial was undertaken to assess ibrutinib treatment in patients with disease marked by 17p deletion or TP53 mutation.² The study enrolled 15 patients (ages 33-82 years) with treatment-naive CLL or SLL and 14 patients (ages 56-79 years) with relapsed or refractory CLL or SLL. Patients received 420 mg ibrutinib daily until disease progression or unacceptable toxicity. During the first 6 months, blood, bone marrow, and lymph node samples were taken for correlative studies. Twothirds of the patients had advanced Rai stage disease, 52% had bulky disease, and 62% had splenomegaly.

Treatment with ibrutinib was generally well tolerated, and most AEs were grade 1 or 2. Grade 3 or higher nonhematologic AEs were reported in 13% of patients and consisted primarily of infections and skin rashes. Hematologic AEs were rare, and no drug discontinuations occurred owing to AEs. Doses were reduced in several patients for AEs such as recurring grade 3 infections, skin rash, and arthralgia. Two deaths occurred on-study, including 1 patient on day 3 and 1 patient during week 7. Both deaths were considered unrelated to study treatment and were presumed to be caused by infection.

With 26 patients evaluable at 6 months, virtually every patient achieved a reduction in lymph node adenopathy, with many patients achieving reductions of 95% in as little as 2 months of treatment with ibrutinib monotherapy. Mean reduction in lymph node size was 70%. Based on criteria from the International Workshop on CLL, 54% of patients achieved a PR, and an additional 42% of patients achieved a PR with lymphocytosis, yielding an ORR of 96%.^{3,4} One

patient had progressive disease, which was presumed to be caused by Richter's transformation 3 weeks into the trial. The estimated 12-month event-free survival rate was 90%.

Ibrutinib treatment typically induces an initial, rapidly escalating rise in peripheral lymphocyte count, which resolves by approximately 3 months. By 6 months of treatment, most patients' lymphocyte counts decreased to either baseline or below baseline. All 22 patients examined also had a reduction in splenomegaly, with a median reduction in spleen volume of 46%. Bone marrow biopsies for 23 patients showed a decrease in tumor burden by a median of 76% based on immunohistochemistry for CD79a, with tumor volume calculated based on the percentage of CD79apositive cells in the bone marrow. In some patients, this analysis showed an almost complete eradication of CLL cells from the bone marrow.

The study also examined the course of 17p deletion in patients receiving ibrutinib, using fluorescence in situ hybridization to monitor chromosome status. In a representative patient with relapsed CLL, the CLL count prior to treatment was $84,000/\mu$ L, with approximately 70% of cells exhibiting 17p deletion. After 6 months of study treatment, the patient showed a reduction in 17p cells of more than 90%, and the total CLL count was 7,000/ μ L. Moreover, based on data from 18 patients, the percentage of CLL cells with 17p deletion generally decreased

ABSTRACT SUMMARY Combinations of the PI3Kδ Inhibitor Idelalisib (GS-1101) With Rituximab and/or Bendamustine Are Tolerable and Highly Active in Patients With Previously Treated, Indolent Non-Hodgkin Lymphoma: Updated Results From a Phase I Study

Idelalisib is an oral inhibitor of PI3Kδ, an isoform of PI3K whose signaling is critical for B cells to activate, proliferate, and survive. This nonrandomized, investigator-choice, phase 1B study allocated patients with indolent lymphoma to 3 different regimens: idelalisib plus rituximab weekly for 8 cycles (31 patients), idelalisib plus bendamustine 90 mg/m² on days 1 and 2 for 6 cycles (34 patients), and idelalisib plus a combination of bendamustine and rituximab (14 patients; abstract 068). The 3 cohorts had similar characteristics. All patients had received prior treatment (median, 3 prior regimens) that included rituximab. Approximately half of the patients completed 48 weeks of idelalisib, with a mean and median duration of dosing of approximately 1 year. Some patients had received idelalisib for more than 2.5 years. The most common AEs were fever, nausea, fatigue, and rash. Cough and gastrointestinal symptoms occurred in approximately one-third of the patients and were usually grade 1 or 2. Pneumonia of grade 3 or 4 occurred in 15%. Liver enzymes were elevated in approximately half of the patients, with enzyme abnormalities of grade 3 or 4 occurring in 16%. Patients receiving the rituximab combination had an ORR of 72%, and ORR in the bendamustine-containing regimens ranged from 71% to 85%. Rates of CR were approximately 25% across the cohorts. Median PFS had not been reached, and the 2-year PFS was 62.5%. PFS was similar across the cohorts. At 24 months, 69% of the responding patients were still in response. This rate was similar across cohorts.

with treatment, from a range of 12% to 97% at baseline to a range of 0% to 92% at 6 months. Fifteen patients experienced a median 55% reduction in cells with 17p deletion; the percentage was unchanged in 1 patient and increased in 3 patients. However, even for the patients with an increase in the proportion of 17p deletion clones, the total lymphocyte counts decreased substantially. The results suggested that malignant B cells harboring the 17p deletion may be more sensitive to ibrutinib treatment than CLL cells with intact 17p.

References

1. Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. *J Clin Oncol.* 2013;31(1):88-94. 2. Wiestner A, Farooqui M, Valdez J, et al. Single agent ibrutinib (PCI-32765) is highly effective in chronic lymphocytic leukaemia patients with 17p deletion [abstract 008]. *Hematol Oncol.* 2013;31(S1).

3. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood.* 2008;111(12):5446-56.

 Cheson BD, Byrd JC, Rai KR, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. *J Clin Oncol.* 2012;30(23):2820-2820.

Updated Results of a Phase I First-in-Human Study of the BCL-2 Inhibitor ABT-199 (GDC-0199) in Patients With Relapsed/ Refractory (R/R) Chronic Lymphocytic Leukaemia (CLL)

The novel therapy ABT-199 is a highly selective and highly potent orally bioavailable BCL2 inhibitor that is being tested in an ongoing phase 1 trial of patients with CLL/SLL or NHL. Seymour and colleagues presented results for the CLL/SLL cohort.¹ There were 2 primary study objectives: to assess safety and pharmacokinetics, and to determine the maximum tolerated dose that could be recommended for phase 2 testing. Secondary objectives included efficacy and identification of biomarkers and pharmacogenetics.

Patients had measurable disease that required therapy. They had relapsed or refractory disease after at least 1 prior standard regimen that included fludarabine or an alkylator. Patients had good performance status and adequate bone marrow. The minimum platelet count was 50,000/mL, which could be obtained via growth factor support in patients with heavily infiltrated bone marrow. Adequate renal function was required. Patients who had received prior high-dose therapy or had active infection were excluded from the study.

In the first cohort, patients received a single dose of ABT-199 200 mg on day minus 3. Starting on day 1 of



Figure 6. In a phase 1 study of the BCL-2 inhibitor ABT-199, among the 30 evaluable chronic lymphocytic leukemia/small lymphocytic lymphoma patients with a peripheral count greater than 5% at entry, the median reduction of peripheral blood lymphocytosis was nearly 90%. Adapted from Seymour J et al. *Hematol Oncol.* 2013;31(suppl 1): Abstract 057.¹

week 1, ABT-199 was administered at 200 mg/day, every day. This regimen was administered to 3 patients, all of whom developed tumor lysis syndrome. This event was not associated with clinical sequelae, and patients were able to continue with treatment. These patients showed rapid tumor reduction, with a greater than 95% reduction in circulating lymphocyte count within 24 hours in 2 patients with baseline lymphocytosis, and rapid reduction in palpable adenopathy. The treatment schedule was modified to have a step-wise dose escalation from cohort 2 onwards. Patients received a single dose of 50 mg on day minus 7. Patients then received 50 mg during week 1 and 150 mg during week 2. In weeks 3 and after, ABT-199 was administered at the final dose. Among patients who were perceived to be at high risk of tumor lysis syndrome by the managing clinician, the initial dose was reduced to 20 mg (n=3), and then they followed the step-wise dose escalation over 3 weeks to the cohort target dose. This treatment schedule was followed by the 53 patients who subsequently entered the trial. Tumor lysis syndrome was reported in 3.

The patients were a median age of 67 years. In 50%, bulky lymphadenopathy exceeded 5 cm, and in 18%, it exceeded 10 cm. The median number of prior therapies was 4, and fludarabine-refractory disease was present in 32% of patients. Deletion 17p was reported in 38%.

ABT-199 was associated with potent tumor reduction; 90% of patients achieved a reduction in the sum of the diameters of more than 50% according to CT criteria. Among the 30 evaluable patients with a peripheral count greater than 5 at entry, the median reduction of peripheral blood lymphocytosis was nearly 90% (Figure 6). The median time to a 50% reduction in nodal size was 43 days in the 51 evaluable patients (Figure 7). Among the 31 patients who underwent bone marrow testing at 24 weeks on study, 28 achieved a greater than 50% reduction.

The ORR was 81%. Eighteen percent of patients achieved either a true complete remission or a complete remission with incomplete peripheral blood count recovery. Those favorable response rates were reproduced in the adverse prognostic subgroups, including those with 17p deletion, with ORRs still at 81%, and 2 of 18 patients achieving complete remission. Among fludarabine-refractory patients, several of whom had 17p deletion, the ORR was similar, at 78%.

Dose-limiting toxicities were seen on the study. After the first cohort, in which tumor lysis syndrome was dose-limiting, there were 4 patients with dose-limiting toxicities. Two of those events were clinical tumor lysis syndrome, 1 in a patient who required dialysis. One death was attributed to tumor lysis syndrome.

Other AEs included grade 3/4 neutropenia in 38%. Most patients responded to treatment with growth fac-



Figure 7. In a phase 1 study of the BCL-2 inhibitor ABT-199, the median time to a 50% reduction in nodal size was 43 days in the 51 evaluable patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. Adapted from Seymour J et al. *Hematol Oncol.* 2013;31(suppl 1): Abstract 057.¹

ABSTRACT SUMMARY Phase 1B Study Combining Ibrutinib With Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in Patients With CD20-Positive B-Cell Non-Hodgkin Lymphoma

This phase 1B study combined ibrutinib with R-CHOP (abstract 069). The enrolled patients, who had previously untreated NHL, received a daily oral dose of ibrutinib at 280 mg (7 patients), 420 mg (4 patients), or 560 mg (6 patients), along with standard doses of R-CHOP. The patients were a median age of 65 years, and 59% were male. A total of 47% had DLBCL, 29% had MCL, and 24% had FL. Dose-limiting toxicity affected 2 patients in the 280 mg cohort, with 1 case of transient syncope and 1 case of periorbital cellulitis. At 560 mg, 1 patient had grade 2 gastritis. The recommended phase 2 dose is 560 mg. The most common AEs, affecting more than 20% of the patients, were neutropenia (77%), thrombocytopenia (65%), vomiting (59%), anemia (53%), nausea (47%), fatigue (35%), headache (29%), constipation (24%), diarrhea (24%), and dizziness (24%). At the time of the report, 6 patients had completed 6 cycles of treatment, and 2 had discontinued treatment. Discontinuations were due to noncompliance with the study drug (n=1) and AEs that were not considered to be dose-limiting toxicities (n=1). Of the 10 patients with at least 1 postbaseline tumor assessment, the ORR was 100%, including 7 CRs and 3 PRs. The combination of ibrutinib and R-CHOP was found to have an acceptable safety profile, and no new toxicities were noted with the combination. A phase 2 study in newly diagnosed DLBCL is opening.

tor. Only 1 patient needed to come off the study because of neutropenia. There were 11 incidences of grade 3/4 thrombocytopenia, but they were not dose-related. Two patients developed reactivation of immune thrombocytopenia.

Reference

1. Seymour J, Davids M, Pagel J, et al. Updated results of a phase I first-in-human study of the BCL-2 inhibitor ABT-199 (GDC-0199) in patients with relapsed/ refractory (R/R) chronic lymphocytic leukaemia (CLL) [abstract 057]. *Hematol Oncol.* 2013;31(suppl 1).

Objective Responses in Relapsed or Refractory B-Cell Lymphomas With Single-Agent Brentuximab Vedotin

n ongoing study is investigating the antitumor activity of brentuximab vedotin in patients with CD30-positive NHL. This study consists of 2 parts: part A is examining single-agent brentuximab vedotin in patients with CD30positive B-cell lymphoma and mature T-/NK-cell lymphomas, and part B is examining brentuximab vedotin in combination with rituximab in patients with CD30-positive B-cell neoplasms. Jacobsen and associates presented results from an interim analysis of patients with CD30-positive B-cell neoplasms, including DLBCL, who have received brentuximab vedotin monotherapy.¹

Patients in the study had CD30positive NHL, including DLBCL and other B-cell subtypes. CD30 expression was determined by immunohistochemistry testing in local laboratories. A retrospective analysis of CD30 expression was performed by a central laboratory. Patients had relapsed/refractory disease after treatment with at least 1 prior systemic therapy. Patients could be as young as 6 years old. They had an ECOG score of 2 or lower or a Lansky score of at least 50.

Brentuximab vedotin was administered at 1.8 mg/kg intravenously every 3 weeks until the occurrence of disease progression or unacceptable toxicity. There was a restage at cycles 2 and 4, and then every 3 cycles thereafter. Disease response was assessed by the investigator according to the Revised Response Criteria for Malignant Lymphoma.² Progressive disease was defined by the Cheson 2007 criteria and by the investigator's assessment.

The primary objective of this analysis was to determine ORR (CR plus PR) in patients with relapsed or refractory CD30-positive NHL. The secondary objectives were to characterize the



Figure 8. In a study of single-agent brentuximab vedotin, 81% of B-cell patients achieved a tumor reduction. CR, complete response; DLBCL, diffuse large B-cell lymphoma. Adapted from Jacobsen E, et al. *Hematol Oncol.* 2013;31(suppl 1): Abstract 304.¹

relationship of CD30 expression with antitumor activity; to assess the duration of tumor control, including duration of response and PFS; and to evaluate safety of treatment with brentuximab vedotin.

The patients' median age was 59.5 years (range, 16 to 83 years), and most were male (57%). Most patients had an ECOG status of 0 (41%) or 1 (48%).

Patients received a median of 3.5 treatment cycles (range, 1-9 cycles). The ORR was 33% (14% CR, 19% PR) among all patients. The median duration of objective response was 24.1 weeks (range, 0.1 + to 48.1 + weeks). Among all B-cell patients, 81% achieved tumor reduction (Figure 8). DLBCL patients (n=25) had a 44% ORR (20% CR, 24% PR). Their median duration of objective response was not reached (range, 0.1+ to 48.1+ weeks). Objective responses were observed in 4 of 8 B-cell NHL subtypes, including elderly patients with DLBCL positive for the Epstein-Barr virus as well as patients with DLBCL-not otherwise specified, grey zone lymphoma, and post-transplant lymphoproliferative disorder.

At the time of the analysis, 14 patients were still receiving treatment.

Reasons for treatment discontinuation included progressive disease (n=22), AEs (n=3), patient decision (n=2), and stem cell transplant (n=1). Grade 3 or higher AEs were reported in 22 patients. Neutropenia was the most frequent event (15 patients, 34%). Three patients (7%) had grade 4 neutropenia. AEs occurring in more than 1 patient also included anemia and leukopenia (2 patients each, 5% each). Other notable events occurring in 1 patient included grade 3 infection and pneumonia and grade 4 febrile neutropenia, GVHD, hypotension, tachycardia, and thrombocytopenia. AEs included grade 3 neutropenia, grade 3 maculopapular rash, and grade 5 unrelated renal failure due to disease progression. Four patients died within 30 days of the last dose; all of these events were considered disease-related.

References

^{1.} Jacobsen E, Bartlett NL, Horwitz SM, et al. Objective responses in relapsed or refractory B-cell lymphomas with single-agent brentuximab vedotin [abstract 304]. *Hematol Oncol.* 2013;31(suppl 1).

^{2.} Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007;25:579-586.

Phase I Study of the Anti-CD79b Antibody-Drug Conjugate DCDS4501A in Relapsed or Refractory B-Cell Non-Hodgkin's Lymphoma

The novel agent DCDS4501A is an ADC with a similar structure to the anti-CD22 ADC, except that the antibody portion in DCDS4501A is directed against CD79b. CD79b is a component of the B-cell receptor and is expressed on the surface of more than 95% of B-cell hematologic malignancies. The ADC is rapidly internalized upon binding. It has shown significant anti-tumor activity in mouse xenograft models of NHL.¹

This phase 1 study consisted of a single-agent dose escalation starting at 0.1 mg/kg and escalating to the MTD of 2.4 mg/kg administered every 21 days.² The study opened single-agent expansion cohorts in indolent NHL and DLBCL. A phase 1B cohort combined the ADC with rituximab at a standard dose. Enrollments in the dose escalation, dose expansion, and phase 1B cohorts were complete at the time of this report. This analysis provided data for patients who were treated at doses of 1.8 mg/kg or higher, which was the minimum dose at which activity was seen.

At baseline, most of the 60 enrolled patients were heavily pretreated, as 75% of them had 3 or more prior systemic therapies. Almost all of the patients had received prior rituximab therapy, and 28% had undergone autologous stem cell transplant therapy. The most common lymphoma of the enrolled patients was DLBCL, followed by FL and MCL.

The AEs that affected more than 10% of the patients and were considered related to the treatment were neutropenia, diarrhea, pyrexia, nausea, peripheral neuropathy, and fatigue. The most common grade 3 and 4 AEs were neutropenia, which was managed by growth factor support, and peripheral neuropathy. Patients in the single-agent arm received a median of 6 treatment cycles, and those in the combination arm received a median of 10 cycles. Approximately one-third of the patients had treatment discontinuations, 13% had dose reductions, and 42% had treatment delays. The most common reasons for treatment discontinuations, reductions, and delays were peripheral neuropathy and neutropenia, which are known side effects of this ADC.

Within 30 days after the last dose of DCDS4501A, 4 deaths occurred. They were due to progressive disease, lung infection, worsening ascites, and a staphylococcus sepsis. None of these deaths were considered attributable to the ADC by the investigator. Peripheral neuropathy, which is a known side effect of this ADC, was reported by 49% of the patients in the single-agent arm and 78% in the combination arm. Most of the peripheral neuropathy was grade 1 or 2 in severity, although 4 patients in the single-agent arm had grade 3 or 4 peripheral neuropathy. The number of days to first peripheral neuropathy was variable, with worsening occurring at a median of 40 to 50 days. Approximately 40% of the patients in both arms reported a reversal of peripheral neuropathy back to baseline levels. At baseline, 18% of the enrolled patients had ongoing peripheral neuropathy.

The pharmacokinetic data were similar to the CD22 ADC data. Notably, the free MMAE drug concentration was 100-fold lower than the conjugated form of the drug. The combination with rituximab did not change the pharmacokinetics of the ADC.

The efficacy of best responses in evaluable patients was assessed by the investigator. In the single-agent arm, 57% of the patients had an objective



Figure 9. In a phase 1 study of the antibody-drug conjugate DCDS4501A in relapsed or refractory B-cell non-Hodgkin's lymphoma, responses improved when the agent was combined with rituximab. CR, complete response; PR, partial response. Data from Palanca-Wessels MC et al. *Hematol Oncol.* 2013;31(suppl 1): Abstract 040.²

response, with 12% having CRs and 45% having PRs. In the combination arm with rituximab, 78% had an objective response, with 22% having CRs and 56% having PRs (Figure 9). On both arms, approximately 20% of the patients had SD.

In the single-agent arm, more than 50% of the patients with DLBCL and 50% with indolent lymphoma had an objective response. Notably, the 5 patients with indolent lymphoma who received the CD79b ADC with rituximab all had responses. Almost all the patients with MCL had a response. The responses were durable. At least 2 patients had been treated for more than 10 months, and they were continuing with treatment and still having a response at the time of this analysis.

In conclusion, DCDS4501A is an anti-CD79b ADC with an acceptable safety profile, as most AEs were grade 1/2. Neutropenia is the most frequent

grade 3/4. Neuropathy was manageable through dose delays, reductions, and discontinuations. The combination of this ADC with rituximab did not show any additional toxicity. The pharmacokinetic profile was acceptable, as the free drug concentration was 100-fold lower than the conjugated form. The addition of rituximab did not impact the pharmacokinetics. Most importantly, anti-tumor activity was seen in this heavily pretreated patient population with relapsed or refractory NHL. Durable responses were observed. The additive effect of rituximab in combination with this ADC still requires additional clarification. Thus, additional clinical evaluation of this ADC in combination with rituximab in B-cell malignancies is ongoing in phase 2 studies.

References

1. Dornan D, Bennett F, Chen Y, et al. Therapeutic potential of an anti-CD79b antibody-drug conjugate, anti-CD79b-vc-MMAE, for the treatment of non-Hodgkin lymphoma. *Blood.* 2009;114:2721-2729.

2. Palanca-Wessels MC, Salles GA, Czuczman MS, et al. Phase I study of the anti-CD79b antibody-drug conjugate DCDS4501A in relapsed or refractory (R/R) B-cell non-Hodgkin's lymphoma (NHL) [abstract 040]. *Hematol Oncol.* 2013;31(suppl 1).

Preliminary Safety and Efficacy of IPI-145, a Potent Inhibitor of Phosphoinositide-3-Kinase-δ,-g, in Patients With Relapsed/Refractory B-Cell Lymphoma

PI-145 is a potent inhibitor of the δ isoform of PI3K, and a very potent inhibitor of the γ isoform (Figure 10). This ongoing phase 1 study aimed to establish a maximum tolerated dose, clinical activity, pharmacokinetics, and pharmacodynamics of IPI-145.¹ The study included patients with multiple hematologic malignancies, although this analysis was limited to patients with B-cell lymphomas.

The key inclusion criteria for this study were relapsed or refractory disease and adequate end organ function. The minimum neutrophil count was 750/mm³, with a minimum platelet count of 75,000/ μ L. This discussion included 2 dose expansion cohorts, which did not have a minimum blood count requirement for inclusion.

The agent was administered orally twice daily in 28-day cycles. The patients began at a dose of 8 mg orally twice a day, and the dose was escalated up to 100 mg orally twice a day. A dose expansion cohort existed in indolent lymphoma and CLL/SLL at 25 mg orally twice a day. The study is currently enrolling another dose expansion cohort at 75 mg orally twice a day. The efficacy data were not complete. Most data were missing from the patients enrolled in the 75 mg orally twice daily arm, who had not been on treatment long enough for assessment. The study enrolled 51 patients with B-cell lymphoma, with 15 in the IPI-145 dose-escalation phase, 16 in the IPI-145 at 25 mg orally twice a day group, and 20 in the IPI-145 at 75 mg orally twice a day group. The median age was 63 years, and 35% of the patients were female. Of the 51 patients, 38 were currently evaluable for efficacy.

The median number of therapies at baseline was 3.5. Patients had discontinued their most recent treatment less than 6 months before enrollment. The median number of prior systemic therapies was 3. Depending on histology, the International Prognostic Index (IPI), the Mantle Cell Lymphoma International Prognostic Index (MIPI), and the Follicular Lymphoma International Index (FLIPI) defined 40% of the patients as high risk at study entry, and 40% had bulky disease.

At the time of this report, the median number of treatment cycles was 4, with months on treatment ranging from 1 to 15. More than 12 months of therapy had been received by 2 patients. A total of 27 patients are continuing to receive therapy and 24 have discontinued therapy. The reasons for discontinuation included progressive disease (13 patients) and AEs (6 patients).

The most common AE was neutropenia, although it turned out to be a



Figure 10. IPI-145 is a potent inhibitor of the δ isoform of PI3-kinase, and a very potent inhibitor of the γ isoform.

relatively clinically insignificant toxicity. Similar to other agents in this class, transaminase elevation was found, and it was manageable with drug holidays and subsequent dose reductions. Other AEs included respiratory infections leading to cough and fever and a smaller proportion of patients with nausea and diarrhea. During cycle 1, some transient, mild-to-moderate neutropenia occurred, but the neutropenia tended to improve over time such that the patients ended up very close to their baseline absolute neutrophil count. Platelet counts were not meaningfully impacted during therapy, and hemoglobin levels tended

to improve on therapy. A total of 23 serious AEs occurred in 16 patients, and 13 of these were considered drug-related. They included 4 pneumonias (2 of which were typical pneumonias and 2 of which appeared to be opportunistic *pneumocystis jiroveci* pneumonia), 2 events of diarrhea, possible drug-induced pneumonitis, zoster, esophagitis, and colitis. Treatment discontinuation due to AEs occurred in 6 patients, and these AEs included 2 events of transaminitis, 1 of disseminated zoster, and 1 of diarrhea. One episode of fatal *P jiroveci* infection occurred, as did 1 fatal episode of febrile neutropenia.

Pharmacokinetic analysis found essentially complete suppression of the PI3K δ isoform and substantial inhibition of the PI3K γ isoform throughout the dosing interval. The drug was rapidly absorbed, with a half-life of 4 to 5 hours.

Among the 26 patients with indolent lymphoma who were treated, 19 were evaluable and 13 responded (68%), with 3 CRs. A minor response occurred in 1 patient with WM, based on Waldenström's criteria. Among the 6 patients with mantle cell lymphoma (MCL), 4 responded, with 1 CR. Among the 3 patients with HL, 1 responded. None of the 10 patients with aggressive lymphoma responded, although 1 patient would have met the criteria for a response but then developed a new lesion that was considered progressive disease. Two patients with indolent lymphoma had progressive disease, and 1 was not evaluable by nodal criteria. The majority of patients, whether or not they were responders, had some clinical benefit from the agent.

The maximum tolerated dose was found to be 75 mg orally twice a day. The pharmacokinetic data suggested that IPI-145 at 25 mg orally twice a day enabled complete suppression of the PI3K δ isoform and strong inhibition of the γ isoform throughout the dosing interval. The drug appears to be well tolerated up to 75 mg orally twice a day. Responses were rapid. An ongoing expansion cohort exists for 75 mg orally twice a day. A phase 2 trial is evaluating IPI-145 at 25 mg orally twice a day in refractory indolent lymphoma.

Reference

1. Kahl BS, Patel M, Younes A, et al. Preliminary safety and efficacy of IPI-145, a potent inhibitor of phosphoinositide-3-kinase-δ,-g, in patients with relapsed/refractory B-cell lymphoma [abstract 066]. *Hematol Oncol.* 2013;31(suppl 1).

Commentary

Craig 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

tith the 2013 meeting, the International Conference on Malignant Lymphoma is now being held every other year in Lugano, Switzerland. Previously, the meeting had been held at 3-year intervals. This increased frequency led to some repetition of studies presented at earlier meetings, including the American Society of Clinical Oncology, the American Society of Hematology, and the previous Lugano conference. There was, however, a significant amount of new information in both non-Hodgkin lymphoma and Hodgkin lymphoma, which will be the focus of this discussion.

Most of the non-Hodgkin lymphoma abstracts evaluated new agents, either in combination with rituximab or as monotherapy. There were many studies in indolent lymphoma and small lymphocytic lymphoma (SLL)/ chronic lymphocytic leukemia (CLL) and an important study in diffuse large B-cell lymphoma. The majority of abstracts in Hodgkin lymphoma provided data on the use of positronemission tomography (PET) from large studies with practice implications. There were also abstracts with early data from ongoing brentuximab vedotin studies.

Non-Hodgkin Lymphoma

A number of abstracts evaluated novel oral agents in non-Hodgkin lymphoma. The 3 novel agents furthest along in clinical development are ibrutinib, idelalisib, and ABT-199. A fourth agent, IPI-145, is approximately a year behind the others. All of these agents have activity. Data were presented on novel antibody-drug conjugates as well.

Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, was the subject of 2 landmark papers published in *The New England Journal of Medicine* in CLL and mantle cell lymphoma.^{1,2} An interesting study presented at the Lugano meeting examined single-agent ibrutinib in patients with CLL who have a 17p deletion.³ It is well known that abnormalities in *p53* portend a very poor prognosis in CLL/SLL, so there is no standard treatment for these patients. Data were presented on the first 29 patients who have been treated in this ongoing study. Interestingly, nearly all the patients had some evidence of response, and more than 80% had improvement in the size of their lymph nodes. When bone marrow tests were repeated, the majority of patients showed a reduction in the number of cells that had the 17p deletion. This study may be the first to show that an agent has significant activity in p53-positive CLL, and one would expect that ibrutinib will be approved for this subset of CLL patients.

Another important non-Hodgkin lymphoma study evaluated rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (R-CHOP) and ibrutinib in diffuse large B-cell lymphoma.⁴ In this phase 1, dose-finding study, the combination was well tolerated with no additive toxicity. The response rate was high. Most of the patients achieved remission, which led to the initiation of a large, international, random-assignment trial comparing R-CHOP and ibrutinib versus R-CHOP alone in the activated B cell-like (ABC) subtype of diffuse large B-cell lymphoma.⁵ This trial, known as DBL3001, is not yet recruiting.

Idelalisib is a PI3K\delta inhibitor. Data were presented by a number of groups regarding the use of idelalisib as a single agent and combined with chemotherapy. The most impressive of these studies, presented by Gilles Salles, MD, PhD, was a large trial of patients with indolent lymphoma who were very heavily pretreated.6 All 125 patients had previously received multiple rituximabbased chemotherapy regimens, including R-CHOP or rituximab/bendamustine. Almost 80% of patients were refractory to more than 2 treatments. Disease histologies included SLL, marginal zone lymphoma, follicular lymphoma, and Waldenström's macroglobulinemia. There was a very impressive response rate of 50%, with some complete responses. Most importantly, in this heavily pretreated patient population, the median progression-free survival was approaching 1 year when the results were

reported. Such a response is unheard of in a patient population that is rituximabrefractory and has received many lines of previous chemotherapy.

Several other studies examined the use of idelalisib in previously treated patients. A study from the Cancer and Leukemia Group B (CALGB) combined idelalisib with rituximab, bendamustine, or both.7 These patients were less heavily pretreated than those in the study by Salles and colleagues.⁶ The study enrolled 79 patients. The overall response rate for the 3 treatment cohorts was 81%, with 27% of patients achieving a complete response. Among the patients who achieved a response, the progression-free survival was 72% at 20 months. This impressive response has led to phase 3 studies involving idelalisib in combination with rituximab, with or without bendamustine.

ABT-199 is a second-generation BCL2 inhibitor that has been evaluated by multiple centers worldwide. John Seymour, MD, presented data from an Australian study that included 56 patients with SLL/CLL.8 Most of the patients were very heavily pretreated. ABT-199 was given at a lower dose with a 1-week washout, which was followed by daily dosing. In an earlier analysis, ABT-199 had been associated with tumor lysis syndrome, and drug development was halted. This association was addressed with a change in the dosing schedule. Among the 54 evaluable patients, 85% had evidence of response, including several complete responses. It is clear that the drug is highly active in CLL/SLL. These studies are ongoing, especially in patients who have 17p deletions and other poor risk factors in CLL.

Inhibition of the PI3 kinase (PI3K) pathway was also explored in a study of IPI-145, a second-generation agent. In distinction to idelalisib, which is a pure δ inhibitor, IPI-145 is a PI3K $\gamma\delta$ inhibitor. In a large, phase 1, dose-escalation study, IPI-145 was given twice daily for 28 days.⁹ The 65 patients had a variety of B-cell lymphoma tumors. The response rate was very adequate at 52%, and

included complete responses. The major toxicity was neutropenia. IPI-145 is continuing in clinical development as a single agent. It will subsequently be combined with other agents in B-cell tumors.

abstracts focused on Several antibody-drug conjugates. Ranjana Advani, MD, presented results from a study evaluating an antibody-drug conjugate to CD22 bound to monomethyl auristatin E, known as DCDT2980S, in non-Hodgkin lymphoma patients who were fairly heavily pretreated.10 The patients received the antibody-drug conjugate alone or combined with rituximab. Unfortunately, the response rates were low: 30% in patients receiving DCDT2980S alone and 33% in patients receiving DCDT2980S and rituximab.

A study presented by Maria Palanca-Wessels, MD, PhD, studied a different antibody-drug conjugate, DCDS4501A, with more encouraging results.¹¹ This anti-CD79B antibodydrug conjugate was administered with or without rituximab to patients with non-Hodgkin lymphoma. The response rates were greater than 50%, with complete responses seen in heavily pretreated patients. Responses were seen in both indolent lymphoma and aggressive lymphoma. Of the 2 antibody-drug conjugates, DCDS4501A is the better one to move forward.

Hodgkin Lymphoma

Oliver Press, MD, presented the first results from the United States intergroup PET-adapted study in patients with advanced-stage Hodgkin lymphoma.12 More than 350 patients were enrolled in this phase 2 study. All patients received 2 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy, and then underwent a PET scan. If the PET scan was negative, ABVD was continued. If the PET scan was positive, the patients received 4 to 6 doses of escalated bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP). Although the follow-up is still short, much has been learned from this study. The PET-negative rate was approximately 80%. Among those patients who had a negative PET scan and who received 6 cycles of ABVD, the 2-year progression-free survival was only 79%, which is suboptimal. Among the patients who were PET-avid-and received escalated BEACOPP-the expected progression-free survival was 61%. I have concerns regarding the low progression-free survival seen in the PET-negative patients. However, this study is pivotal in our thinking of whether the addition of brentuximab vedotin to doxorubicin, vinblastine, and dacarbazine (AVD) can improve outcome compared with ABVD alone, especially in patients who have a negative interim PET scan. An ongoing, international, random-assignment trial is examining this question.¹³

Our group presented the results of a PET-adapted sequential therapy program with brentuximab vedotin and augmented ifosfamide, carboplatin, and etoposide (ICE) for salvage therapy in patients with relapsed and refractory Hodgkin lymphoma.14 All the patients were in first relapse or had primary refractory disease. They underwent 6 doses of weekly brentuximab vedotin, followed by a repeat PET scan. If the PET scan was negative, the patients went directly to transplant and received no salvage chemotherapy. If the PET scan remained positive, the patients underwent augmented ICE chemotherapy and subsequently went to transplant. Of note, among the first 30 patients enrolled, 29 have gone to transplant successfully, and 80% of the patients are in remission. This study will likely finish in mid-2014.

Lastly, Robert Chen, MD, presented an update of their study evaluating nonmyeloablative allogeneic stem-cell transplant in patients with Hodgkin lymphoma who have previously been treated with brentuximab vedotin.¹⁵ A brief report was published by Chen and colleagues in Blood showing a 1-year progression-free survival in this setting that exceeded 90%.¹⁶ With longer follow-up, those curves have decreased. Nearly two-thirds of the patients were progression-free after receiving brentuximab and a nonmyeloablative allogeneic transplant. This outcome is dramatically better than that seen in the pre-brentuximab era. It will likely be a new standard of therapy for patients to receive short-course brentuximab vedotin prior to a nonmyeloablative allogeneic transplant.

Acknowledgment

Dr Moskowitz has received research support from and is on the Scientific Advisory Boards of Seattle Genetics and Pharmacyclics.

References

1. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med. 2013;369(1):32-42. 2. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013;369(6):507-516. 3. Wiestner A, Farooqui M, Valdez J, et al. Single agent ibrutinib (PCI-32765) is highly effective in chronic lymphocytic leukaemia patients with 17p deletion [abstract 008]. Hematol Oncol. 2013;31(suppl 1). 4. Younes A, Flinn I, Berdeja J, et al. Phase 1B study combining ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in patients with CD20-positive B-cell non-Hodgkin lymphoma [abstract 069]. Hematol Oncol. 2013;31(suppl 1). 5. Pharmacyclics.com. Pharmacyclics reports second quarter 2013 results. http://ir.pharmacyclics.com/ releasedetail.cfm?releaseid=781773. Posted July 31, 2013. Accessed August 8, 2013.

6. Salles GA, Kahl BS, de Vos S, et al. Interim results from a phase II study of PI3Kd inhibitor idelalisib in patients with relapsed indolent non-Hodgkin lymphoma refractory to both rituximab and an alkylating agent [abstract 064 bis]. *Hematol Oncol.* 2013;31(suppl 1).

 Leonard JP, Wagner-Johnston ND, Coutre SE, et al. Combinations of the PI3Kδ inhibitor idelalisib (GS-1101) with rituximab and/or bendamustine are tolerable and highly active in patients with previously treated, indolent non-Hodgkin lymphoma: updated results from a phase I study [abstract 068]. *Hematol* Oncol. 2013;31(suppl 1).

8. Seymour J, Davids M, Pagel J, et al. Updated results of a phase I first-in-human study of the BCL-2 inhibitor ABT-199 (GDC-0199) in patients with relapsed/ refractory (R/R) chronic lymphocytic leukaemia (CLL) [abstract 057]. *Hematol Oncol.* 2013;31(suppl 1).

9. Kahl BS, Patel M, Younes A, et al. Preliminary safety and efficacy of IPI-145, a potent inhibitor of phosphoinositide-3-kinase-δ,-g, in patients with relapsed/refractory B-cell lymphoma [abstract 066]. *Hematol Oncol.* 2013;31(suppl 1).

10. Advani R, Chen A, Lebovic D, et al. Phase I study of the anti-CD22 antibody-drug conjugate (ADC) DCDT2980s with or without rituximab in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma [abstract 039]. *Hematol Oncol.* 2013;31(suppl 1).

11. Palanca-Wessels MC, Salles GA, Czuczman MS, et al. Phase I study of the anti-CD79b antibody-drug conjugate DCDS4501A in relapsed or refractory (R/R) B-cell non-Hodgkin's lymphoma (NHL [abstract 040]). *Hematol Oncol.* 2013;31(suppl 1).

12. Press O, LeBlanc M, Rimsza LM, et al. A phase II trial of response-adapted therapy of stage III-IV Hodgkin lymphoma using early interim FDG-PET imaging: U.S. Intergroup S0816 [abstract 124]. *Hematol Oncol.* 2013;31(suppl 1).

 ClinicalTrials.gov. Brentuximab vedotin plus AVD in limited-stage Hodgkin lymphoma. http:// clinicaltrials.gov/show/NCT01534078. Identifier: NCT01534078. Accessed August 8, 2013.

14. Moskowitz AJ, Schoder H, Gerecitano J, et al. PETadapted sequential therapy with brentuximab vedotin and augmented-ICE induces FDG-PET normalization in 92% of patients with relapsed and refractory Hodgkin lymphoma [abstract 141]. *Hematol Oncol.* 2013;31(suppl 1).

15. Chen R, Forman S, Palmer J, et al. Two-year followup of patients with relapsed/refractory Hodgkin treated with brentuximab vedotin prior to reduced intensity allogeneic hematopoietic cell transplantation [abstract 140]. *Hematol Oncol.* 2013;31(suppl 1).

16. Chen R, Palmer JM, Thomas SH, et al. Brentuximab vedotin enables successful reduced-intensity allogeneic hematopoietic cell transplantation in patients with relapsed or refractory Hodgkin lymphoma. *Blood.* 2012;119(26):6379-6381.

Leaders in antibody-drug conjugate development

Extending the reach of our technology through collaboration

Company

AbbVie

Agensys, a subsidiary of Astellas Pharma Bayer

Celldex Therapeutics

Daiichi Sankyo

Genentech, a member of the Roche Group

Genmab

GlaxoSmithKline

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 tumorassociated antigen that has restricted expression on normal cells.^{1,2}

OSeattleGenetics[®]

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.**

REFERENCES: 1. Carter PJ, Senter PD. Antibody-drug conjugates for cancer therapy. *Cancer J.* 2008;14(3):154-169. 2. Senter PD. Potent antibody drug conjugates for cancer therapy. *Curr Opin Chem Biol.* 2009;13(3):235-244. 3. Polson AG, Calemine-Fenaux J, Chan P, et al. Antibody-drug conjugates for the treatment of non–Hodgkin's lymphoma: target and linker-drug selection. *Cancer Res.* 2009;69(6):2356-2364.

Seattle Genetics and to are US registered trademarks of Seattle Genetics, Inc. © 2013 Seattle Genetics, Inc., Bothell, WA 98021 All rights reserved. Printed in USA USP/COR/2013/0001(1)