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Brentuximab Vedotin (SGN-35)

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Brentuximab Vedotin (SGN-35)

Jessica Katz[1], John E. Janik[2], and Anas Younes[3]

Abstract

Brentuximab vedotin (SGN-35) is an antibody-drug conjugate (ADC) directed against the CD30 antigen expressed on Hodgkin lymphoma and anaplastic large cell lymphoma. SGN-35 consists of the cAC10 chimerized IgG1 monoclonal antibody SGN30, modified by the addition of a valine-citrulline dipeptide linker to permit attachment of the potent inhibitor of microtubule polymerization monomethylauristatin E (MMAE). In phase II trials, SGN-35 produced response rates of 75% in patients with Hodgkin lymphoma ($n = 102$) and 87% in patients with anaplastic large cell lymphoma ($n = 30$). Responses to SGN-35 might be related not only to the cytotoxic effect due to release of MMAE within the malignant cell but also to other effects. First, SGN-35 may signal malignant cells through CD30 ligation to deliver an apoptotic or proliferative response. The former would amplify the cytotoxicity of MMAE. A proliferative signal delivered in the context of MMAE intoxication could enhance cell death. Second, the efficacy of SGN-35, particularly in Hodgkin lymphoma, might be attributed to its effect on the tumor microenvironment. Diffusion of free MMAE from the targeted tumor cells could result in a bystander effect that kills the normal supporting cells in close proximity to the malignant cells. The elimination of T regulatory cells that inhibit cytotoxic effector cells and elimination of cells that provide growth factor support for Hodgkin/Reed–Sternberg cells could further enhance the cytotoxic activity of SGN-35. Here we review the biology of SGN-35 and the clinical effects of SGN-35 administration. *Clin Cancer Res; 17(20); 6428–36. ©2011 AACR.*

Introduction

Monoclonal antibodies have emerged as a major focus for drug development for cancer treatment since rituximab and trastuzumab received approval in the late 1990s. Rituximab, the first monoclonal antibody approved for the treatment of cancer, produced regression of lymphadenopathy in ~50% of patients with relapsed follicular lymphoma (1). However, although they can produce significant clinical benefits, particularly when administered with chemotherapy, monoclonal antibodies alone do not produce long-lasting clinical benefit. Early attempts to improve the therapeutic efficacy of monoclonal antibodies prompted the addition of linkers that allowed the conjugation of radioisotopes for delivering high doses of radiation to the site of the tumor. This strategy resulted in the U.S. Food and Drug Administration (FDA) approving 2 agents, ibritumomab tiuxetan (Zevalin; Spectrum Pharmaceuticals) and ^{131}I tositumomab (Bexxar; GlaxoSmithKline), for the treatment of relapsed B-cell lymphoma (2–5). An alternative strategy, modification of antibodies to deliver chemotherapeutic agents to tumors, required a more prolonged developmental pathway to address the large number of factors that can affect the therapeutic efficacy of these molecules (6–10). Gemtuzumab ozogamicin (Mylotarg; Pfizer) was the first antibody-drug conjugate (ADC) to be approved for the treatment of cancer, but it was withdrawn from the market in 2010 for lack of efficacy and increased patient deaths (11). Despite this setback, ADCs now appear poised to play a major role in cancer treatment (12).

CD30 Biology

CD30 is an attractive target for monoclonal antibody therapy because of its limited expression on normal tissues and its uniform, high-level expression on malignant cells in patients with classical Hodgkin lymphoma and anaplastic large cell lymphoma (ALCL; ref. 13). Expression of CD30 is associated with T-cell activation. In lymph nodes, it is expressed in the parafollicular areas, in the rim of the follicular center, and on centroblasts within the germinal centers (14). CD30-positive cells are also found in the medulla of the thymus. Both T and B cells may be positive for CD30 expression, which is more commonly observed in proliferating cells. It has been reported that 3% to 31% of peripheral blood lymphocytes, most of which are

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CD8-positive and produce IFN-γ and interleukin (IL)-4, express CD30 (15). Other normal cells that express CD30 include macrophages, activated natural killer cells, endothelial cells, and decidual cells. Lymphoid cells infected with Epstein–Barr virus, human T-cell leukemia virus, or *Herpesvirus saimiri* may express high levels of CD30.

CD30 is a member of the TNF receptor (TNFR) superfamily, which comprises more than 25 members, including the TNF receptors Fas, CD40, and RANK (16, 17). A protein analysis of CD30 showed an 18-residue leader peptide followed by a 365-amino-acid extracytoplasmic domain, a 24-amino-acid transmembrane region, and a cytoplasmic tail of 188 amino acids (14). Signaling through the TNFR superfamily of molecules affects cellular proliferation, survival, and differentiation, and these effects are mediated through the cytoplasmic domains of the receptors (18). TNFR1 and Fas contain an 80-amino-acid motif, designated the death domain, that induces apoptosis through interaction with Fas-associated death domain (FADD) and TNFR-associated death domain (TRADD), which in turn recruit caspases to initiate the apoptotic cascade. In contrast, TNFR1 can activate NF-κB to prevent cell death through the interaction of TNFR1, TRADD, and TNFR-associated factor 2 (TRAF2). CD30 does not contain a death domain but is able to produce an apoptotic stimulus. The mechanism for this effect is thought to be related to the degradation of TRAF2, which prevents its interaction with the TNFR1-TRADD complex, thereby enhancing death signaling through the TNFR (Fig. 1; ref. 16). CD30 ligand and monoclonal antibodies that interact with this signaling portion of the molecule are thought to induce apoptosis by initiating CD30 signaling without concurrent NF-κB activation (discussed below). The constitutive NF-κB activity associated with classical Hodgkin lymphoma prevents the apoptosis induced in ALCL.

Antibody-Drug Conjugates

ADCs combine the specificity of targeting inherent to monoclonal antibodies with the ability to deliver highly toxic chemotherapeutic agents that cannot be administered systemically. SGN-35 consists of the cAC10 monoclonal antibody (SGN30) modified by the addition of a dipeptide linker to permit attachment of microtubule polymerization monomethylauristatin E (MMAE). The protease-sensitive dipeptide linker is composed of citrulline and valine. Two to 8 linkers are attached per molecule of cAC10 monoclonal antibody, with the most prevalent species containing 4 molecules. The advantage of the dipeptide linker is that it provides maximal serum stability with efficient hydrolysis and release of MMAE by human cathepsin B (Fig. 2A; ref. 19). The features that determine the safety and efficacy of ADCs are described by Teicher and Chari (12) in their overview of ADCs in this *CCR Focus* section.

Proteins are internalized by cells through phagocytosis, macropinocytosis, caveolae-mediated endocytosis, clathrin-mediated endocytosis, and clathrin- and caveolin-independent endocytosis (20). Phagocytosis is restricted to specialized cell types, such as macrophages and neutrophils, and has little role in ADC effects. Similarly, macropinocytosis results in uptake of extracellular proteins in a concentration-dependent fashion and, thus, would not provide significant therapeutic advantage compared with free drugs. Both caveolae- and clathrin-mediated uptake have

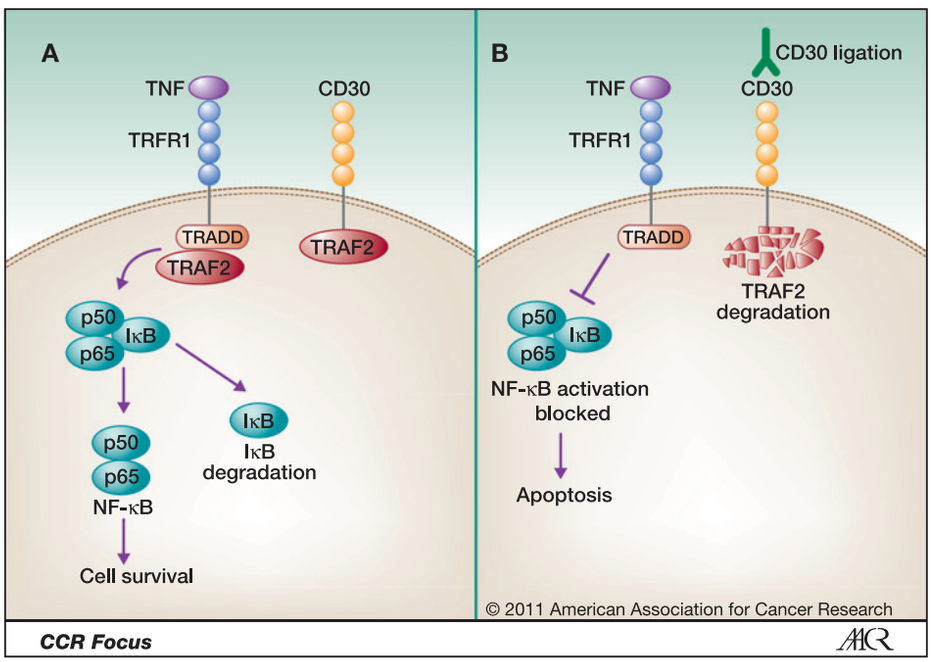

Figure 1. CD30 signaling. A, TRAF2 interacts with CD30 and TRADD bound to the cytoplasmic domain of TNFR1. TNFR1 signaling through TRADD and TRAF2 interaction produces a prosurvival signal through activation of NF-κB. B, ligation of CD30 results in TRAF2 degradation, depleting TRAF2 and making it unavailable to interact with TRADD. In the absence of TRAF2, NF-κB is not activated, and TNF signaling will preferentially activate apoptotic pathways. The constitutive activation of NF-κB in some cases of classical Hodgkin lymphoma may account for the lack of activity with SGN-30 alone.

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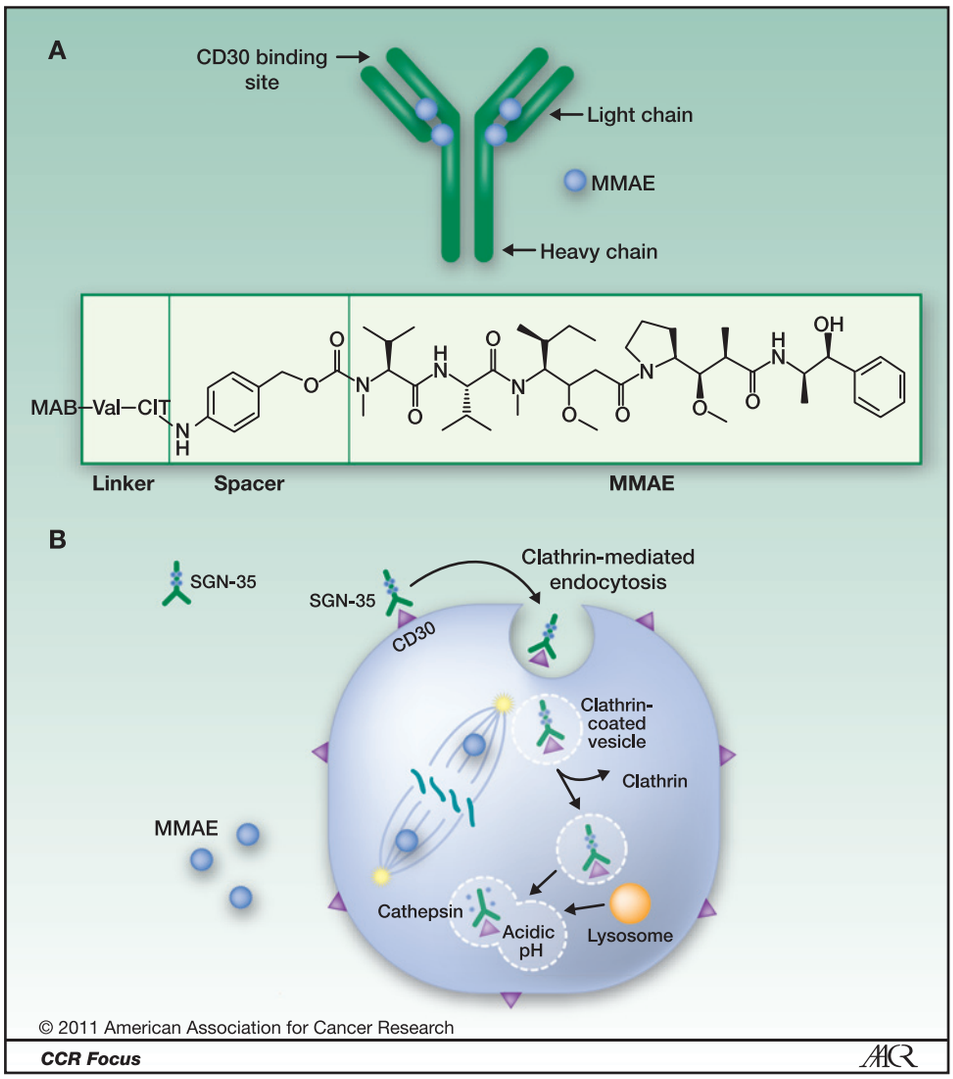

Figure 2. A, SGN-35 structure. MMAE is attached to the IgG1 monoclonal antibody cAC10 by sulfhydryl groups in cysteine residues. A mild reduction of the interchain disulfides is used to attach the citrulline-valine dipeptide linker. A variable number of drug molecules are attached, ranging from 2 to 8, with 4 being the most prevalent. B, ADC internalization process. SGN-35 is internalized following binding to cell surface CD30 by clathrin-mediated endocytosis. The clathrin-coated vesicle is uncoated to allow fusion with lysosomes, and clathrin recirculates to the cell surface. In the acidic milieu of the vesicle, cathepsin cleaves the citrulline-valine dipeptide linker to release free MMAE. MMAE binds to microtubules to prevent mitosis, and free MMAE can diffuse out to the cell to produce cytotoxicity in the tumor microenvironment.

been described for monoclonal antibodies, but the former results in trafficking to the Golgi or endoplasmic reticulum. The proteolytic enzymes required to release the conjugated drug do not exist within these organelles. The failure to release conjugated MMAE would, therefore, limit the therapeutic efficacy of caveloae-mediated uptake. Internalization of SGN-35 and other ADCs is primarily the result of clathrin-mediated uptake (Fig. 2B). Within the cytoplasm, the clathrin-coated pit is stripped of clathrin, which is recirculated to the cell surface. The internalized ADC within the uncoated pit is joined to a lysosomal vesicle that contains proteolytic enzymes. The lysosomal protein cathepsin releases MMAE from the dipeptide linker of SGN-35, and the free MMAE is available to bind tubulin to prevent its polymerization. A small fraction diffuses out of the targeted tumor cell, allowing it to exert cytotoxic effects on surrounding cells in the tumor microenvironment (6). The latter event may contribute significantly to the efficacy of SGN-35.

Anaplastic Large Cell Lymphoma: Diagnosis and Clinical Presentation

ALCL is a T-cell non-Hodgkin lymphoma that accounts for 40% of pediatric non-Hodgkin lymphoma and <5% of

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adult lymphomas (21). It is characterized by large, atypical tumor cells, known as the hallmark cells, which usually have vesicular horseshoe- or kidney-shaped nuclei with prominent nucleoli. Two major variants of ALCL are distinguished based on the expression of anaplastic lymphoma kinase (ALK) and, thus, are termed ALK-positive and ALK-negative ALCL. ALK expression most commonly results from the translocation of the ALK gene on chromosome 2 into the nucleophosmin (*NPM*) gene on chromosome 5. This translocation produces an 80-kDa NPM-ALK fusion protein with constitutive tyrosine kinase activity. Other fusion partners have been described that result in ALK positivity with tyrosine kinase activation. All ALCLs are CD30-positive, and the hallmark cell can stain for EMA, clusterin, and CD25 (expressed on all ALK-positive tumors but variably expressed on ALK-negative tumors) (22).

Patients with ALK-positive ALCL have a markedly better prognosis than those with ALK-negative ALCL, but this may be driven largely by the age of the patients (21). The survival of patients with ALK-negative ALCL was reported to be similar to that of patients with peripheral T-cell lymphoma in an early study (23), but a more recent international collaboration showed that the ALK-negative group has a significantly better outcome than the peripheral T-cell lymphoma group (21).

Classical Hodgkin Lymphoma: Diagnosis and Clinical Presentation

Hodgkin lymphoma is a B-cell lymphoproliferative malignancy that usually presents as solitary or generalized lymphadenopathy. Most patients present with painless lymph node enlargement. Pathologically, classical Hodgkin lymphoma is distinguished from other lymphomas by the presence of large binucleated or multinucleated cells with prominent nucleoli, known as Hodgkin/Reed–Sternberg (HRS) cells, surrounded by a benign reactive host response consisting of various immune components. Immunostaining for CD30 and CD15 can help to clarify the diagnosis. Evidence regarding the origin of HRS cells suggests that they are derived from a preapoptotic germinal B cell. They often develop mutations that prevent functional surface immunoglobulin rearrangements, which, along with decreased B-cell–specific transcription factors and B-cell–receptor signaling, prevent surface immunoglobulin expression. Studies of the molecular pathogenesis of classical Hodgkin lymphoma suggest several mechanisms that inhibit apoptosis (24–26). First, although caspase 3 is expressed by HRS cells, it is not active. The extrinsic pathway of apoptosis is blocked by the c-FLICE inhibitory protein, and the intrinsic pathway is blocked by the X-linked inhibitor of apoptosis proteins. Second, HRS cells may constitutively express NF-κB. Third, a history of Epstein–Barr virus infection is associated with increased risk of classical Hodgkin lymphoma. HRS cells show a specific expression pattern of viral-latent genes with expression of latent membrane protein (LMP)1 and 2a, as well as Epstein–Barr nuclear antigen. LMPs are important because evidence suggests that they have transforming potential in epithelial cells. LMP1 can upregulate the *BCL-2* gene and other activation-associated genes.

The Rye classification divides classical Hodgkin lymphoma into 4 subtypes based on the ratio of neoplastic to reactive cells: lymphocyte-rich, nodular sclerosis, mixed cellularity, and lymphocyte-depleted. In Western countries, the most common presentation of classical Hodgkin lymphoma is nodular sclerosis Hodgkin lymphoma (~70% of cases), followed by mixed cellularity (20–25%), lymphocyte-rich (5%), and lymphocyte-depleted (1%). Overall cure can be achieved in 80% of patients with combination chemotherapy and radiation.

Clinical Trial Data Targeting CD30

Hodgkin lymphoma and ALCL were evaluated in studies that used 2 different unconjugated monoclonal antibodies

Table 1. Summary of responses to CD30-directed therapies

	SGN-30 (ref. 27)	MDX-060 (ref. 28)	SGN-35 every 3 weeks	SGN-35 weekly (ref. 48)
Hodgkin lymphoma				
Doses	6 or 12 mg/kg weekly	1–15 mg/kg	1.8 mg/kg every 3 weeks	0.4–1.4 mg/kg
Number of patients	35	47	102	22
Response rate	0	8% ORR (4% CR, 4% PR)	75% ORR (34% CR, 40% PR)	41% ORR (27% CR)
ALCL				
Doses	6 or 12 mg/kg weekly	1–15 mg/kg	1.8 mg/kg every 3 weeks	0.4–1.4 mg/kg
Number of patients	41	7	30 of 58 evaluable	5
Response rate	17% ORR (5% CR, 12% PR)	28% ORR (28% CR)	87% ORR (57% CR, 30% PR)	80% ORR (80% CR)

Abbreviations: CR, complete remission; ORR, overall response rate; PR, partial remission.

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to target CD30, SGN-30, and MDX-060 (Table 1). SGN-30 (also known as cAC10) is a chimerized IgG1 monoclonal antibody used to generate SGN-35. MDX-060 is a fully human monoclonal antibody and has greater antibody-dependent, cell-mediated cytotoxicity. Studies with both unconjugated antibodies were not promising, and further development has been curtailed because of the low response rate. A phase II study of SGN-30 was done to determine the safety and objective response rate (27). Each treatment consisted of 6 weekly infusions with a 2-week treatment-free period. The patients had received a median of 3 prior regimens. Although the treatment was tolerable and safe at the 2 doses tested (6 or 12 mg/kg), the response rate was low. In the ALCL group, 2 of 41 patients (5%) achieved complete remission (CR), and 5 of 41 patients (12%) achieved partial remission (PR). The clinical benefit rate (CR, PR, and stable disease) achieved was 31%. The duration of response ranged from 27 to >1,460 days. There were no objective responses in the classical Hodgkin lymphoma group, although 29% of the patients achieved stable disease. MDX-060 was tested in a phase I–II study to determine safety, maximum tolerated dose (MTD), and efficacy in patients with relapsed or refractory CD30-positive lymphomas (28). Seventy-two patients (63 with classical Hodgkin lymphoma, 7 with ALCL, and 2 with T-cell lymphoma) were enrolled in the study. Although the overall response rate (ORR) in the classical Hodgkin lymphoma group was 6% (4 of 63 patients), the ORR in the ALCL group was 29% (2 of 7 patients). The 2 ALCL patients (both with predominant skin disease) achieved CR.

SGN-35 was evaluated in a phase I clinical trial in 45 patients with relapsed or refractory CD30-positive hematologic malignancies (29). This trial was designed as a dose-escalation study to determine the MTD followed by a cohort expansion phase. A secondary objective was to study the pharmacokinetics, i.v. and antitumor activity of SGN-35. SGN-35 was administered i.v. every 3 weeks. The subjects were permitted to continue therapy until progressive disease or unacceptable toxicity occurred. The median age of patients in the study was 36 years. Ninety-three percent of the patients had classical Hodgkin lymphoma and 4% had ALK-positive ALCL. All patients had received prior chemotherapy (median of 3), and 73% had undergone a prior autologous stem cell transplant. Treatment doses ranged from 0.1 to 3.6 mg/kg. The most common adverse events were fatigue (36%), fever (33%), diarrhea (22%), nausea (22%), neutropenia (22%), and peripheral neuropathy (22%), followed by headache, vomiting, back pain, anemia, and alopecia. Most adverse events were grades 1 and 2. The MTD of SGN-35 given every 3 weeks was determined to be 1.8 mg/kg. At this dose, only 1 of 12 patients experienced a dose-limiting toxicity of grade 4 thrombocytopenia. At the 2.7-mg/kg dose level, 3 of 12 patients experienced dose-limiting toxicities, including hyperglycemia, unrelated acute renal failure, and unrelated prostatitis and febrile neutropenia. A single patient treated at a dose of 3.6 mg/kg developed febrile neutropenia and died of infectious complications. At 1.8 mg/kg, 4 of 12 patients (33%) experienced CR and 2 of 12 patients (16%) experienced PR. At 2.7 mg/kg, 6 of 12 patients (50%) experienced CR and 1 patient had PR. Tumor regression, as observed by computed tomography, was reported for 36 of 42 evaluable patients (83%). Of 16 patients with symptoms at baseline, 13 (81%) had resolution during treatment, regardless of response status. Although there were only 2 patients with ALCL, they both achieved CR.

The results of a pivotal phase II study of SGN-35 in relapsed or refractory Hodgkin lymphoma were reported at the 2011 Annual Meeting of the American Society of Clinical Oncology (ASCO; 30). In this study, 102 patients with refractory or relapsed classical Hodgkin lymphoma received a 1.8 mg/kg dose of SGN-35 every 3 weeks. The median age of the patients was 31 years, and most patients were classified with an Eastern Cooperative Oncology Group performance score of 0 to 1. All patients had undergone a prior autologous stem cell transplant, and the median number of previous therapies was 4. The median duration of treatment on this study was 27 weeks. The most common treatment-related adverse events were sensory peripheral neuropathy, nausea, neutropenia, diarrhea, and pyrexia. Ninety-seven patients (95%) had a reduction in tumor volume. The ORR was 75%, with 34% and 40% of patients achieving CR and PR, respectively. The median duration of response for patients achieving CR had not been reached and ranged up to 61 weeks. The efficacy of SGN-35 in relapsed or refractory systemic ALCL was also updated at the 2011 ASCO meeting. The results of a phase II single-arm study involving 58 patients were presented. The ORR was 86%, with CR in 53% of patients. The median duration of response had not been met. Of 15 patients with malignant cutaneous lesions at baseline, 93% had resolution of all lesions. The median time to resolution was ~5 weeks. Adverse events remained manageable. Most of the patients (70%) had ALK-negative tumors. Re-treatment of relapsed patients with an initial primary response with SGN-35 was retrospectively examined across 3 studies (31). Seven patients received 8 re-treatments. A response was observed in 6 of 8 patients (2 CRs and 4 PRs). Responses occurred between 5 and 13 weeks after re-treatment. Although this is a small subset, it shows that responses can be achieved with re-treatment.

These impressive results must be considered in the context of other treatments for relapsed classical Hodgkin lymphoma and ALCL. In a retrospective review, vinblastine alone produced a response rate of 59% in patients with relapsed Hodgkin lymphoma following autologous transplantation (32). In a similar study, vinblastine alone was evaluated in relapsed or refractory ALCL, with 25 of 30 evaluable patients achieving CR (33). The randomized comparisons described below serve to illustrate the importance of this new agent in the treatment of classical Hodgkin lymphoma, but they leave unanswered the question of whether vinblastine alone could produce an equally efficacious result.

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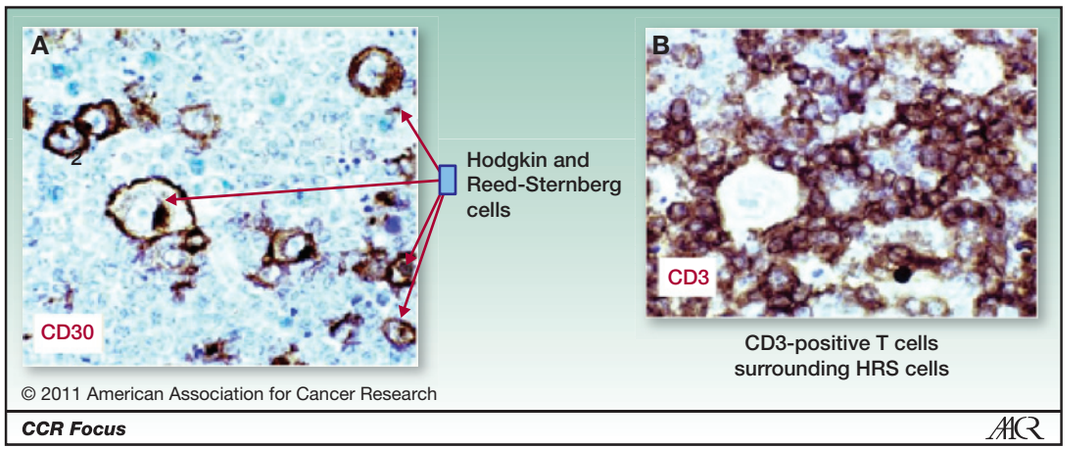

Figure 3. A, Hodgkin lymphoma stained for CD30. B, Hodgkin lymphoma stained for CD3.

In April 2010, a multicenter randomized phase III trial of SGN-35 (the AETHERA trial) was initiated in posttransplant classical Hodgkin lymphoma patients at high risk for recurrence. The study will compare SGN-35 given i.v. every 21 days for ~1 year versus placebo. The primary objective is progression-free survival. Secondary outcome measures include overall survival, incidence of adverse events, and immunogenicity. The study is expected to be completed in June 2013. Another recently initiated study will evaluate the feasibility of adding SGN-35 to standard ABVD chemotherapy in patients with newly diagnosed classical Hodgkin lymphoma.

On July 14, 2011, the Oncology Drug Advisory Committee of the FDA unanimously recommended that SGN-35 receive accelerated approval for the treatment of Hodgkin lymphoma that has relapsed after autologous stem cell transplant and for the management of relapsed ALCL. On August 19, 2011, as this *CCR Focus* section was going to press, the FDA approved SGN-35 [brentuximab vedotin; now marketed as Adcentris (Seattle Genetics)] for these indications, making it the first approved drug for Hodgkin lymphoma in 30 years. The results of the AETHERA trial will form the basis for full FDA approval. Alternative strategies for full registration would include a randomized comparison of the addition of SGN-35 with standard chemotherapy regimens, such as ICE, in relapsed Hodgkin lymphoma, with an endpoint of CR in preparation for autologous transplantation. The importance of achieving CR before transplantation to cure relapsed Hodgkin lymphoma is well established. The ability of SGN-35 in combination with chemotherapy to enhance the CR rate would provide a clinically relevant endpoint and, if successful, would increase the number of patients who would be eligible for transplantation. Furthermore, the durable CR observed with SGN-35 alone raises the question of whether autologous transplantation is necessary for all patients. Studies to evaluate this option might be considered. Incorporation of SGN-35 into the upfront management of Hodgkin lymphoma and ALCL will require studies to assess the toxicity profile of SGN-35 administered with standard regimens, such as ABVD and CHOP. Randomized comparisons with and without SGN-35 will be necessary to show superiority in the initial management of these lymphomas.

Alternative Mechanisms of Action of SGN-35

SGN-35 has shown a significantly higher response rate than other ADCs and immunotoxins (11, 34–36). In a study targeting her-2, as discussed in this *CCR Focus* section (36), trastuzumab emtansine produced a response rate of 26% to 35%. Inotuzumab ozogamicin (CMC-544), which targets CD22, produced an ORR of 39% in relapsed lymphoma, but only 15% of subjects with diffuse large cell lymphoma responded (37). SAR3419, an ADC that targets CD19 with the maytansanoid derivative DM4, produced a 29% response rate in patients with relapsed B-cell lymphoma (38). Another study showed that the coexpression of CD21 on CD19-positive target cells decreased the internalization of the ADC, and selection of subjects with low or negative CD21 expression could enhance efficacy (39). These studies highlight the impressive response rate of SGN-35 and suggest that additional actions may be associated with its use. In general, the HRS cells make up only a small fraction of the tumor mass, and the histology of the tumor shows an abundant fibrotic and inflammatory reaction. Inflammatory cells are recruited to the tumor site by cytokines and chemokines produced by the HRS cells and other cells in the microenvironment that support the proliferation and survival of the malignant HRS cells (40, 41). As shown in Fig. 3, the HRS cells are rosetted by $CD4^+$ T cells that in many cases are positive for expression of CD25. These $CD4^+$, $CD25^+$ cells express CTLA4 and produce IL-10, both of which provide a supportive environment for tumor expansion and have the function of T regulatory cells (42). To provide additional therapeutic benefit, these immunosuppressive T cells might be killed because

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of the bystander effect mediated by diffusion of free MMAE from the targeted HRS cells. Elimination or reduction in the T regulatory cell numbers could allow cytotoxic T cells to exert a beneficial effect against the HRS cells. Diffusion of free MMAE into the microenvironment surrounding the malignant HRS cells could also kill cells that produce growth factors and other cytokines that stimulate proliferation of the malignant HRS cells or that induce antiapoptotic gene expression by the HRS cells. From this, one could predict that patients with grade II nodular sclerosing classical Hodgkin lymphoma, in which the malignant cells sheet out and constitute a larger proportion of the tumor mass, would be less likely to respond. Radioimmunoconjugates offer the potential to target the microenvironment of the tumor because of the crossfire effect of the attached radionuclide, as described in this *CCR Focus* section by Steiner and Neri (43). The path length of the released β electron particle kills not only the tumor cell but also the supporting stroma. With this approach, it is unnecessary for the target cell to express the antigen; instead, cells in the microenvironment can be used as the target. The efficacy of this approach was shown in a study of yttrium-labeled daclizumab, targeting CD25 on the normal T cells that rosette the malignant Hodgkin cells. Among 30 patients with relapsed Hodgkin lymphoma who were treated, there were 12 CRs and 7 PRs, for an ORR of 63% (44). Younes and colleagues (45) and Oki and Younes (46) showed that rituximab produces responses in relapsed Hodgkin lymphoma even though expression of CD20 by Hodgkin cells is infrequent.

Another potential mechanism that may account for the clinical activity associated with SGN-35 stems from its ability to mimic CD30 ligation. CD30 ligation can initiate apoptosis or, alternatively, deliver a proliferative signal to CD30-expressing cell lines (16, 17). The apoptotic activity of CD30 ligation was first shown with HeFi-1 and M44 monoclonal antibodies (47). Both of these antibodies interact with the ligand-binding site of CD30, whereas Ber-H2, which binds to a separate epitope, was inactive in this assay. The apoptotic effect of CD30 ligation was shown with the Karpas 299 and Michel ALCL lines. The classical Hodgkin lymphoma cell lines yielded different results, with only rare cell lines showing apoptosis and others showing a proliferative response. These *in vitro* results mirror the clinical effects obtained with antibodies targeted to CD30, as described above. Little or no clinical activity was seen with MDX-060 or SGN-30 in classical Hodgkin lymphoma, whereas some tumor responses, although marginal, were more commonly observed in patients with ALCL. SGN-35 could augment the cytotoxic effect of MMAE released within the malignant tumor cell by delivering an additional apoptotic signal, principally in ALCL tumor cells where CD30 ligation is known to induce apoptosis. In contrast, a proliferative signal delivered through CD30 ligation in HRS cells could increase the therapeutic effect of the intracellular MMAE by preventing mitosis in a cell that has been stimulated to proliferate. These different mechanisms highlight the need for a better understanding of the effects of SGN-35, which can be achieved only by obtaining tumor biopsies before and after treatment with SGN-35.

Conclusions

The novel ADC SGN-35 induced unprecedented responses in CD30-positive refractory and relapsed hematologic malignancies that may be related to the patient population investigated or to the linker or chemotherapeutic agent used for the construct. There may also be alternative explanations. In this article, we identify 2 potential mechanisms that may be responsible the greater efficacy produced with SGN-35. First, a targeted binding of SGN-35 increases apoptosis in CD30-positive tumor cells. This is especially important in ALCL, where most of the cells within the tumor mass are CD30-positive cells and delivery of an apoptotic signal is expected. CD30 monoclonal antibodies may induce proliferation, as described in Hodgkin lymphoma cell lines, and the delivery of MMAE in the context of a proliferative signal may enhance apoptosis. Second, once it is liberated from the monoclonal antibody, free MMAE can diffuse from the cell into the surrounding stroma, resulting in a bystander effect. This has special relevance for Hodgkin lymphoma, in which the inflammatory and immune cells that make up most of the tumor mass provide growth factor support and help the malignant HRS cells avoid immune recognition. The activity of agents that in general do not target the malignant cells in Hodgkin lymphoma (radiolabeled daclizumab and rituximab) suggests a role for the microenvironment in maintaining the viability of malignant Hodgkin lymphoma cells. Clinically, SGN-35 appears to be safe and tolerable in the heavily pretreated patient populations studied to date. Most studies reported to date enrolled subjects who were 30 to 40 years of age. Further studies of this agent are needed in older populations in which the lower toxicity profile compared with current standard-of-care regimens will be important. Efforts to combine SGN-35 with standard chemotherapy agents are underway. It is hoped that such treatments will improve the CR rate and duration of response, as well as increase our ability to cure these malignancies. However, management of overlapping toxicities with agents commonly used in Hodgkin lymphoma and ALCL will have to be tested. SGN-35 could be the first drug approved for relapsed or refractory CD30-positive hematologic malignancies; it holds significant promise for a patient population for which there is little to offer.

Disclosure of Potential Conflicts of Interest

Drs. Katz and Janik are employed by Bristol-Myers Squibb. Dr. Younes received research support and hororaria from Seattle Genetics. The opinions expressed reflect those of the authors.

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