Expert Opinion

Brentuximab Vedotin (SGN-35), an antibody–drug conjugate for the treatment of CD30-positive malignancies

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Introduction: CD30-positive hematological malignancies are potentially curable with frontline combination chemotherapy regimens; however, those patients who relapse or are refractory to initial therapies have less favorable prognosis.

Areas covered: Brentuximab vedotin is an antibody–drug conjugate (ADC) composed of the anti-CD30 chimeric IgG1 monoclonal antibody cAC10 and the potent antimicrotubule drug monomethylauristatin E connected by a protease-cleavable linker. Treatment with single-agent brentuximab vedotin resulted in unprecedented objective response rates and complete response rates of 75 and 34%, respectively, in relapsed or refractory Hodgkin lymphoma, and of 86 and 57%, respectively, in relapsed or refractory systemic anaplastic large-cell lymphoma patients. Peripheral sensory neuropathy and neutropenia were observed with brentuximab vedotin but were generally grade 1 and 2 in severity and manageable. In August 2011, brentuximab vedotin was approved in the US for the treatment of Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multiagent chemotherapy regimens in ASCT-ineligible candidates, and for the treatment of systemic anaplastic large-cell lymphoma after failure of at least one prior multiagent chemotherapy regimen.

Expert opinion: These data support an expanded development program for brentuximab vedotin in multiple CD30-positive indications.

Keywords: anaplastic large-cell lymphoma, antibody–drug conjugate, brentuximab vedotin, cAC10, CD30, Hodgkin lymphoma, monomethyl auristatin E, SGN-35, TNFSFR8

*Expert Opin. Investig. Drugs (2012) **21**(1):205-216*

1. Introduction – The treatment of CD30-expressing lymphomas

1.1 Hodgkin lymphoma

The use of combined chemotherapy and radiotherapy has dramatically improved the outcomes of patients with Hodgkin lymphoma (HL) over the past 30 years. Commonly used frontline therapies, such as ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), result in complete remission (CR) rates of up to 80 – 90% [1,2]. However, following multimodality frontline therapy, relapse is observed in up to 50% of advanced-stage cases. An additional 5 – 20% of patients are refractory to frontline treatment [3-5]. Current treatment options for patients with relapsed or refractory disease are limited, offer modest clinical benefit and carry high morbidity [6,7]. Multiagent chemotherapy followed by autologous stem cell transplant (ASCT) remains a widely advocated therapy in Western countries for patients whose disease has failed to

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10.1517/13543784.2011.641532 © 2012 Informa UK, Ltd. ISSN 1354-3784

Article highlights.

- Tumor CD30 expression is observed in a subset of aggressive lymphomas that develop frequently recurrent disease for which current salvage therapy offers little benefit.
- Brentuximab vedotin (ADCETRIS) demonstrated an unprecedented high rate of response in early studies in relapsed and refractory HL and sALCL as well as tolerability and manageable toxicity.
- Multiple avenues remain to be explored including the activity of single-agent brentuximab vedotin in relapsed and refractory pre-stem cell transplant HL patients as well as the optimal dose and combination regimens for the use of brentuximab vedotin in frontline and second-line HL and NHL settings.
- Additional work is also required to further explore the differential expression of CD30 in lymphoma subtypes in order to identify patient populations in which this therapy may be of benefit.

This box summarizes key points contained in the article.

respond to frontline therapy; however, more than 20% of those patients are transplant ineligible and another 50% will eventually relapse again despite second-line therapy [1,6-9]. The reasons for transplant ineligibility are multiple and include older age and poor performance status. In addition, limitations in ASCT access and its cost are worldwide health-economics issues.

Patients with relapsed HL post-ASCT fare dismally [10-12]. Patients whose disease progresses within 1 year after ASCT experience the poorest prognosis, with a median overall survival (OS) of only 1.2 years [10,13].

1.2 Anaplastic large-cell lymphoma

Anaplastic large-cell lymphoma (ALCL) is a very rare disease that accounts for approximately 3% of the cases of adult non-Hodgkin lymphoma (NHL) [14,15]. There are two major distinct presentations of ALCL: a systemic disease (sALCL) involving lymph nodes and/or extranodal sites (gastrointestinal tract, soft tissues, lung, liver, bone) and a primary cutaneous form (pcALCL) [16-18]. Primary cutaneous ALCL has an indolent presentation with primarily skin-related symptoms, whereas sALCL commonly has an advanced-stage presentation characterized by lymphadenopathies, associated extranodal infiltrates and bone marrow involvement [19]. While approximately 80% of sALCL patients achieve an objective response (OR) with frontline anthracycline-based therapy, 40 – 65% of patients develop recurrent disease after initial chemotherapy [20], and the long-term prognosis for these patients is poor. The overall 5-year survival rate following initial diagnosis is approximately 30 – 49% for patients with anaplastic lymphoma kinase (ALK)-negative sALCL and 65 – 90% for patients with ALK-positive disease [20-22].

1.3 CD30 expression in HL and ALCL

HL is histopathologically defined by the presence of mononuclear Hodgkin cells and multinucleated Hodgkin Reed–Sternberg cells in a background of a variable mix of non-neoplastic inflammatory cells. Hodgkin Reed–Sternberg cells express the CD30 antigen in nearly all cases [23]. sALCL tumors present with large blastic CD30-expressing cells with horseshoe-kidney-shaped nuclei, the so-called hallmark cells that are present in all sALCL variants [19,24,25]. The CD30 antigen is also expressed in some cutaneous T-cell lymphomas (CTCLs), other NK and T-cell neoplasms, a subset of B-cell lymphomas and embryonal carcinoma [26]. CD30 is a transmembrane glycoprotein receptor member of the tumor necrosis factor (TNF) receptor superfamily 8 (TNFRSF8). The functions of CD30 are not completely understood. Its distribution on normal cells is restricted to activated T and B cells and macrophages [27-30], where it appears to act as an activator of the canonical and alternative nuclear factor-κB (NF-κB) pathways, transducing a cell survival signal [31-34]. Recent data suggest that this receptor may play a role in thymic negative selection [35,36].

2. Brentuximab vedotin

Brentuximab vedotin (SGN-35, ADCETRIS™) is a CD30-directed antibody–drug conjugate (ADC) consisting of three components: i) the monoclonal chimeric antibody cAC10 that is specific for human CD30, ii) the potent antimicrotubule agent monomethyl auristatin E (MMAE) and iii) a protease-cleavable linker that covalently attaches MMAE to cAC10 (**Figure 1**) [37-41]. The biologic activity of brentuximab vedotin results from a multistep process. Binding of the ADC to CD30 on the cell surface initiates internalization of the ADC–CD30 complex, which then traffics to the lysosomal compartment where MMAE is released via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces the mitotic spindle cell-cycle checkpoint and results in growth arrest and apoptotic death of the CD30-expressing tumor cells (**Figure 2**) [37-39,42].

3. Clinical studies of brentuximab vedotin

3.1 Early clinical development program

Clinical evaluation of brentuximab vedotin in patients with relapsed or refractory CD30-positive hematological malignancies was initiated in 2006. The early clinical development program included two Phase I dose-escalation studies (SG035-0001, SG035-0002) [40,43] and also included two Phase I clinical pharmacology studies: an intensive cardiac safety (QT/QTc interval) study (SGN35-007) and a drug–drug interaction/excretion study (SGN35-008). All completed and ongoing brentuximab vedotin studies are summarized in **Table 1**.

The determination of the recommended Phase II dose of brentuximab vedotin, of 1.8 mg/kg every 3 weeks (q3 weeks), was informed by the safety findings of study SG035-0001, in

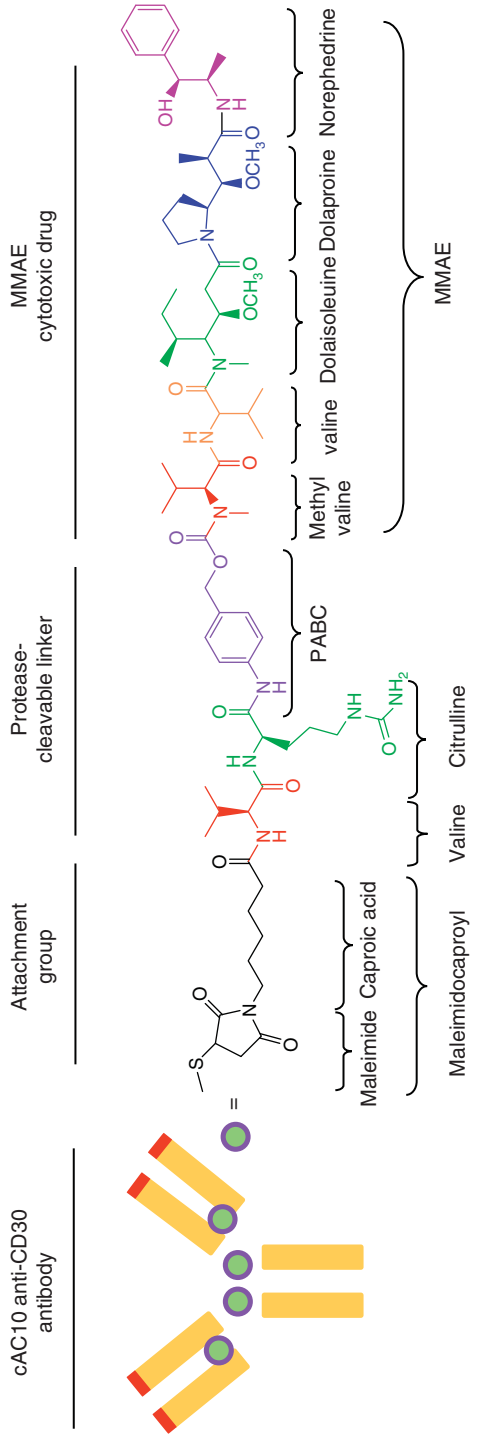

Figure 1. Structure of brentuximab vedotin.

which 45 patients with relapsed or refractory CD30-positive lymphoma (42 HL, 2 sALCL, 1 angioimmunoblastic T-cell lymphoma) were treated with brentuximab vedotin, administered intravenously (i.v.) q3 weeks, at doses ranging from 0.1 to 3.6 mg/kg [40]. These patients had received a median of three prior regimens, and 73% had previously undergone ASCT. Dose-limiting toxicities (DLTs) were reported in five patients. Of 6 patients in the 1.8 mg/kg dose-escalation cohort, 1 experienced a grade 4 thrombocytopenia, but no additional DLTs were reported on expansion of this dose cohort to 12 patients. By contrast, 3 of 12 patients in the 2.7 mg/kg cohort experienced four DLTs; one of the first six dose-escalation patients had unrelated grade 3 acute renal failure, and of the six additional expansion patients, one reported grade 3 hyperglycemia, and another had both unrelated grade 3 prostatitis and grade 3 febrile neutropenia. The one patient treated in the 3.6 mg/kg cohort experienced grade 5 febrile neutropenia and presumed septic shock. In addition, fewer treatment-related and severe adverse events were seen in patients treated at the 1.8 mg/kg dose level as compared with those treated at the 2.7 mg/kg dose level, including fewer cases of neutropenia, thrombocytopenia, anemia and neutropenic fever [40]. Consequently, the maximum tolerated dose (MTD) and recommended Phase II dose were defined as 1.8 mg/kg i.v. q3 weeks. Among all 45 patients, the OR rate (ORR) per investigator was 38%, which included 24% CR. A further 19 of 44 (43%) evaluable patients achieved stable disease (SD), with any tumor regression observed in 36 of 42 (86%) evaluable patients [40]. Among 28 evaluable patients treated at doses of ≥ 1.2 mg/kg, the ORR was 54%. Responses were durable, with a median duration of response (DOR) of at least 9.7 months and a median progression-free survival (PFS) of 5.9 months [40].

In a second Phase I study, SG035-0002, 44 patients with relapsed or refractory CD30-positive lymphoma (38 HL, 5 sALCL, 1 angioblastic T-cell lymphoma) were treated with brentuximab vedotin i.v. on days 1, 8 and 15 of 28-day cycles, at doses of 0.4 – 1.4 mg/kg [43]. The MTD using this dosing schedule was determined to be 1.2 mg/kg. DLTs included grade 3 diarrhea and vomiting, and grade 4 hyperglycemia [43]. Among 39 evaluable patients, the ORR was 56%, including 33% CR; responses were seen in 17 of 33 (52%) HL patients, with nine of them (27%) achieving a CR, and all four sALCL patients who responded achieved a CR [43].

In summary, the results of these Phase I trials demonstrated encouraging activity with brentuximab vedotin and a tolerable safety profile in advanced, aggressive, CD30-positive hematological malignancies and provided a strong rationale for the initiation of a registration program in these disease settings. Based on these Phase I data, the 1.8 mg/kg q3 week dose was used in the Phase II studies.

3.2 Phase II studies

The efficacy of brentuximab vedotin using the 1.8 mg/kg q3-week regimen was formally investigated in two parallel

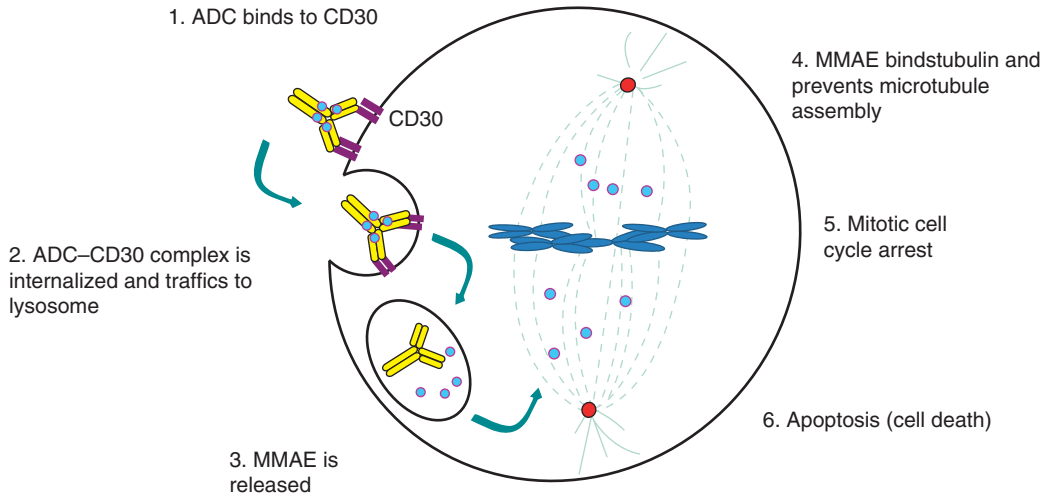

Figure 2. Mechanism of action of brentuximab vedotin.

single-arm studies conducted in relapsed or refractory HL post-ASCT (SG035-0003) [44,45] and relapsed or refractory sALCL (SG035-0004) [46,47]. The outcomes of these studies indicate the preliminary effectiveness of brentuximab vedotin and are described below.

3.2.1 *Study SG035-0003 in HL*

Study SG035-0003 enrolled 102 patients with relapsed or refractory HL who had received prior ASCT [44,45]. Patients were relatively young (median age 31 years) and, importantly, had overall baseline characteristics consistent with an advanced, relapsed or refractory HL population [44,45]. Patients had received a median of 3.5 (range 1 – 13) prior systemic chemotherapy regimens, and 43 (42%) were refractory to their most recent prior therapy. Seventy-two patients (71%) were considered to be primary refractory, defined according to the German Hodgkin Lymphoma Study Group criteria as having failed to achieve a CR or experiencing disease progression within 3 months of completing frontline therapy. Moreover, 72 patients (71%) had experienced relapse within 1 year of their ASCT. Thus, the study population largely consisted of patients with an extremely poor prognosis.

Despite these baseline characteristics, patients received a median of 9 (range 1 – 16) cycles of treatment and 76 (75%) experienced an OR, as assessed by an independent review facility (IRF) according to the revised Response Criteria for Malignant Lymphoma [48], with a median DOR of 6.7 months [44,45]. Thirty-five patients (34%) achieved a CR, with a median DOR in these patients of 20.5 months [44,45]. Analyses of efficacy based on investigator assessment of response were concordant with those based on IRF assessment [49]. Importantly, nearly all patients (94%) experienced some benefit as demonstrated by a measurable reduction in tumor volume (**Figure 3**). Median PFS was 5.8 months based on IRF assessment [44,45], with greater clinical benefit seen among patients achieving a CR; median PFS was 21.7, 5.1, 3.5 and 1.2 months among patients achieving CR, partial remission (PR), SD and progressive disease (PD), respectively [44,45]. Median OS was not reached after approximately 1 year of follow-up; the estimated 12-month OS rate was 89% [44,45].

Additional evidence of clinical benefit was provided by an analysis of B-symptom resolution; 29 of 35 (89%) patients who had one or more B symptoms at baseline had resolution of all symptoms during brentuximab vedotin treatment [49]. Median time to resolution in these patients was 3 weeks (range < 1 – 16 weeks) [49]. In addition, brentuximab vedotin treatment enabled subsequent allogeneic SCT, an exploratory treatment approach employed with the intent to secure prolonged disease control, in five of the patients who achieved a CR [44,45]. Furthermore, in a prespecified correlated survival analysis comparing PFS with brentuximab vedotin per investigator assessment and PFS with patients' most recent post-ASCT prior systemic therapy, among 57 patients with at least one post-ASCT systemic therapy [49], PFS was significantly prolonged with brentuximab vedotin compared with prior systemic therapy (7.8 vs 4.1 months; HR, 0.40; $p < 0.0001$).

3.2.2 *Study SG035-0004 in sALCL*

A total of 58 patients with relapsed or refractory sALCL were enrolled in study SG035-0004. Median age was 52 years (range 14 – 76) and 72% of patients had ALK-negative disease [46,47]. Baseline characteristics were reflective of a patient population with advanced, relapsed or refractory sALCL [46,47]. Patients had received a median of two prior chemotherapy regimens (range 1 – 6), 62% had primary refractory disease, 50% were refractory to their most recent prior therapy and 22% had never achieved an OR with prior therapy [46,47].

Notably, 50 (86%) patients achieved an OR, including 33 (57%) who achieved a CR by IRF assessment, and nearly all patients, 56 (97%), achieved some degree of tumor reduction [46,47]. ORR and CR rate were similar in both ALK-negative and ALK-positive patients [50]. Median DOR was

Table 1. Summary of brentuximab vedotin studies.

Study no./phase	Design	Objective	Diagnosis	Dosage/duration*	Primary endpoint	Planned/ treated/ analyzed‡,§	M:F Med. age (range)	Dates¶/CSR status	Sites#/location
Registration program									
SG035-0001 (NCT00430846) Phase I	Open-label, single-arm, dose escalation	Safety	$CD30^+$ hematological malignancies	0.1 – 3.6 mg/kg i.v. q3 wk/NA	AEs; laboratory abnormalities	51/45/45	62%:38% 36 (20 – 87)	Nov 2006 – Jul 2009/ Final	4/US
SG035-0002** (NCT00649584) Phase I	Open-label, single-arm, dose escalation	Safety	$CD30^+$ hematological malignancies	0.4 – 1.4 mg/kg i.v. q1 wk/12 cycles	AEs; laboratory abnormalities	72/44/44	70%:30% 33 (12 – 82)	Mar 2008 – Feb 2010/Final	5/US
SG035-0003 (NCT00848926) Phase II	Open-label, single-arm	Efficacy and safety	HL	1.8 mg/kg i.v. q3 wk/16 cycles	ORR	100/102/102	47%:53% 31 (15 – 77)	Feb 2009 – Aug 2010/Final	25/US, Canada, W. Europe
SG035-0004 (NCT00866047) Phase II	Open-label, single-arm	Efficacy and safety	sALCL	1.8 mg/kg i.v. q3 wk/16 cycles	ORR	55/58/58	57%:43% 52 (14 – 76)	Jun 2009 – Aug 2010/Interim/Jan 2011 efficacy addendum	22/US, Canada, W. Europe
SGN35-007 (NCT01026233) Phase I	Open-label, single-arm	Clinical pharmacology	$CD30^+$ hematological malignancies	1.8 mg/kg i.v. q3 wk/16 cycles	Duration of ventricular repolarization	48/52/46	48%:52% 34.5 (19 – 76)	Feb 2010 – July 2010/ Interim	9/US, W. Europe
SGN35-008A (NCT01026415) Phase I	Open-label, nonrandomized, three-arm, drug-drug interaction, excretion	Clinical pharmacology	$CD30^+$ hematological malignancies	1.2 or 1.8 mg/kg i.v. q3 wk/2 cycles	PK parameters	36/56/45	59%:41% 33.5 (16 – 71)	Dec 2009 – June 2010/Final	7/US
Additional ongoing clinical studies									
SGN35-005/ AETHERA (NCT01100502) Phase III	Randomized, double-blind, two-arm, placebo-controlled	Efficacy and safety	HL (high-risk post-ASCT)	1.8 mg/kg or placebo i.v. q3 wk/16 cycles	Progression-free survival	322/23	≥ 18	Apr 2010/enrolling	69/US, E. Europe, W. Europe

*Maximum treatment duration represented as treatment cycles (1 cycle = q3 wk, 1 dose/21-day cycle; or q1 wk, 3 doses/28-day cycle; or q2 wk, 2 doses/28-day cycle).

‡Contributed to evaluation of the primary endpoint.

§Enrolled as of 30 September 2010 (additional ongoing studies).

¶First patient visit to date of last assessment for submission/first visit of first enrolled patient.

#Active sites as of 12 January 2011 (additional ongoing studies).

**Designed as two-part dose-escalation study of monotherapy followed by combination therapy (with gemcitabine); study was terminated prior to initiating combination therapy cohorts.

‡‡A separate named-patient program was initiated in November 2010 to provide EU and rest-of-world SGN-35 access.

§§Study SGN35-010 also provides the option of treatment with SGN-35 for patients in the study SGN35-005 who received placebo and experienced HL progression; accordingly, patient enrollment information pertinent to maintaining the sponsor treatment-blind in study SGN35-005 is not presented.

ABVD: Doxorubicin, bleomycin, vinblastine, dacarbazine; AEs: Adverse events; ASCT: Autologous stem cell transplantation; CHOP: Cyclophosphamide, doxorubicin, vincristine, prednisone; CSR: Clinical study report; E: Eastern; F: Female; HL: Hodgkin lymphoma; i.v.: Intravenous; LyP: Lymphomatoid papulosis; M: Male; MF: Mycosis fungoides; NA: Not applicable; ORR: Overall response rate; PK: Pharmacokinetic; sALCL: Systemic anaplastic large-cell lymphoma; SS: Sézary syndrome; W: Western.

Table 1. Summary of brentuximab vedotin studies (continued).

Study no./phase	Design	Objective	Diagnosis	Dosage/duration*	Primary endpoint	Planned/ treated/ analyzed‡,§	M:F Med. age (range)	Dates¶/CSR status	Sites#/location
SGN35-006 (NCT00947856) Phase II	Open-label, nonrandomized, two-arm	Safety and efficacy	CD30+ hematological malignancies	1.2 or 1.8 mg/kg i.v. q3 wk/NA	AEs; laboratory abnormalities; ORR	125/73	≥ 12	July 2009/ enrolling	15/US, W. Europe
SGN35-012 (NCT01421667) Phase II	Open-label, nonrandomized, single-arm	Efficacy and safety	CD30+ non-Hodgkin lymphoma (relapsed)	1.8 mg/kg i.v. q3 wk/NA	ORR	55	≥ 6	August 2011/enrolling	US
SGN35-008B (NCT01026415) Phase I	Open-label, nonrandomized, hepatic or renal impairment	Clinical pharmacology	CD30+ hematological malignancies	1.2 mg/kg i.v. q3 wk/2 cycles	PK parameters	12/5	≥ 18	Jan 2010/ enrolling	7/US
SGN35-009 (NCT01060904) Phase I	Open-label, single-arm, dose-escalation with ABVD	Safety	HL (treatment-naïve)	0.6, 0.9 or 1.2 mg/kg i.v. q2 wk/6 cycles	AEs; laboratory abnormalities	40/13	≥ 18, ≤ 60	Jan 2010/ enrolling	3/US, Canada
SGN35-011 (NCT01309789) Phase I	Open-label, nonrandomized, three-arm, with CHOP	Safety	sALCL (treatment naive)	0.8, 1.2 or 1.8 mg/kg i.v. q3 wk/16 cycles	AEs; laboratory abnormalities	60/0	≥ 18	Planned	0
SGN35-010 (NCT01196208) Expanded Access Program	Open-label, treatment option	Safety and US expanded access‡‡	HL/sALCL	1.8 mg/kg i.v. q3 wk/NA	AEs	380/–§§	≥ 6	Sep 2010/enrolling	50/US, E. Europe, W. Europe
NCT01396070 pilot study	Open-label, single-arm	Efficacy, safety	MF, SS	1.8 mg/kg i.v. q3 wk/8 – 16 cycles	Response rate	18/–	≥ 18	June 2011/enrolling	2/US
NCT01352520 Phase II	Open-label, single-arm	Efficacy, safety	Cutaneous ALCL, MF, LyP	1.8 mg/kg i.v. q3 wk/16 cycles	Response rate	35/–	≥ 18	June 2011/enrolling	1/US

*Maximum treatment duration represented as treatment cycles (1 cycle = q3 wk, 1 dose/21-day cycle; or q1 wk, 3 doses/28-day cycle; or q2 wk, 2 doses/28-day cycle).

‡Contributed to evaluation of the primary endpoint.

§Enrolled as of 30 September 2010 (additional ongoing studies).

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‡‡A separate named-patient program was initiated in November 2010 to provide EU and rest-of-world SGN-35 access.

§§Study SGN35-010 also provides the option of treatment with SGN-35 for patients in the study SGN35-005 who received placebo and experienced HL progression; accordingly, patient enrollment information pertinent to maintaining the sponsor treatment-blind in study SGN35-005 is not presented.

ABVD: Doxorubicin, bleomycin, vinblastine, dacarbazine; AEs: Adverse events; ASCT: Autologous stem cell transplantation; CHOP: Cyclophosphamide, doxorubicin, vincristine, prednisone; CSR: Clinical study report; E: Eastern; F: Female; HL: Hodgkin lymphoma; i.v.: Intravenous; LyP: Lymphomatoid papulosis; M: Male; MF: Mycosis fungoides; NA: Not applicable; ORR: Overall response rate; PK: Pharmacokinetic; sALCL: Systemic anaplastic large-cell lymphoma; SS: Sézary syndrome; W: Western.

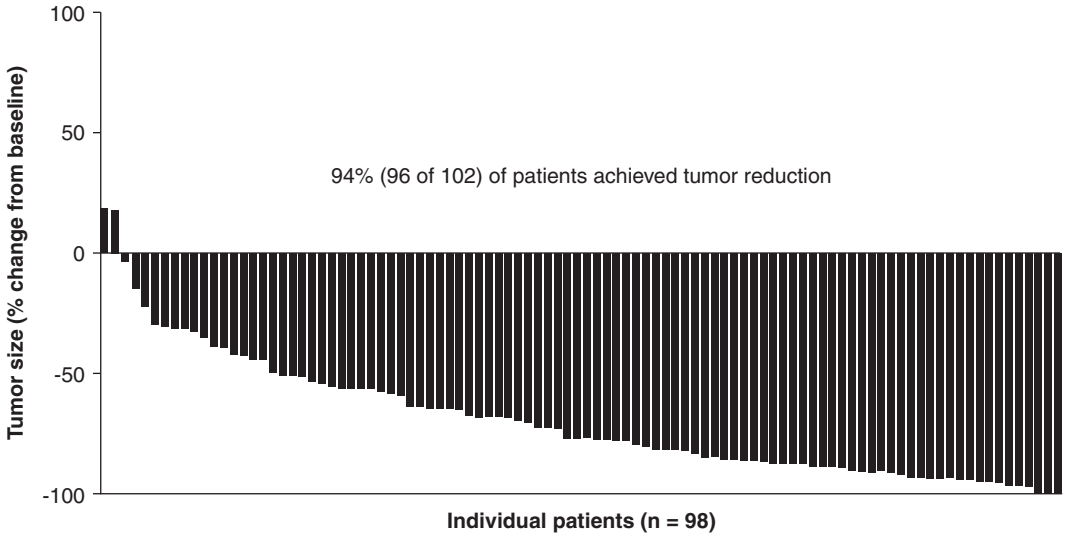

Figure 3. Waterfall plot showing change in tumor size from baseline among individual assessable patients enrolled in study SG035-0003 [45].

12.6 months overall and 13.2 months in patients achieving a CR [46,47]. Among 15 patients with malignant cutaneous lesions at baseline, 13 achieved a CR, 2 achieved a PR and 14 (93%) experienced complete resolution of those lesions, with a median time to resolution of 4.9 weeks (range 2.6 – 36.1) [51]. The median PFS was 13.3 months, and the median OS was not reached at the time of data cutoff for this study [46,47]. An analysis of PFS by response to treatment showed median PFS of 14.6, 4.2, 2.7 and 1.2 months in patients achieving CR, PR, SD and PD, respectively.

As in the HL study, additional evidence of clinical benefit was shown by B-symptom resolution; 14 of 17 (82%) patients had resolution of B symptoms during brentuximab vedotin treatment [50]. Similarly, 14 patients were able to proceed to ASCT (n = 7) or allogeneic SCT (n = 7) immediately following brentuximab vedotin treatment [50]. Furthermore, investigator-assessed median PFS with brentuximab vedotin (14.3 months) was significantly longer compared with that with last prior therapy (5.9 months, multiagent chemotherapy or ASCT in 91%) (HR 0.48, p = 0.001) [46,47].

3.3 Retreatment with brentuximab vedotin

A case series analysis of patients with relapsed or refractory HL (n = 7) or sALCL (n = 1) who were enrolled in Phase I or II studies of brentuximab vedotin demonstrated that retreatment with this agent is feasible and provides repeated reductions in tumor burden [42]. Among eight patients, three of whom were retreated twice, the ORR was 64% (seven responses to 11 retreatments), which included two CRs. Time to response was 5 – 15 weeks [42]. Also B symptoms resolved in four out of six patients [42]. These findings suggest that tumor sensitivity to brentuximab vedotin continues following an initial course of treatment.

3.4 Brentuximab vedotin post-allogeneic stem cell transplant

A second case series analyzed the utility of brentuximab vedotin as treatment for 25 HL patients who had relapsed post-allogeneic SCT [52]. Although allogeneic SCT represents a potentially curative option for relapsed or refractory HL, a high proportion of patients subsequently relapse [53] and require further effective therapies. Median patient age was 32 years (range 20 – 56). Patients had received a median of five prior regimens (range 2 – 12) and received a median of eight cycles (range 1 – 16) of brentuximab vedotin 1.2 or 1.8 mg/kg q3 weeks. Among 24 evaluable patients, 12 (50%) achieved an OR, including 9 (38%) who achieved a CR. A further 10 (42%) achieved SD [52]. Responses occurred in a median of 1.9 months, and median PFS was 7.8 months [52]. These findings suggest that brentuximab vedotin has notable activity in heavily pretreated post-allogeneic SCT HL patients.

4. Safety profile of brentuximab vedotin

Data from the studies reviewed herein indicate that brentuximab vedotin has good tolerability, with generally manageable toxicity consisting of primarily mild or moderate peripheral neuropathy, neutropenia and infusion reactions. In the two Phase II studies in HL and sALCL, adverse events led to treatment discontinuation in 21% of patients [41] and no treatment-related deaths were reported [44-47].

4.1 Peripheral neuropathy

Peripheral neuropathy (PN) was the most notable adverse event associated with brentuximab vedotin treatment. PN appeared cumulative and dose dependent, consistent with that observed with other antimicrotubule agents [54,55].

Overall, in the Phase II studies in HL and sALCL, 54% of patients experienced any-grade treatment-emergent PN, which was primarily of mild-to-moderate severity [41,44-47]. The most frequently reported PN events were sensory neuropathy (44%), motor neuropathy (9%), paresthesia (4%) and demyelinating polyneuropathy (1%) [44-47]. Grade 3 events occurred in 18 patients (11%) and consisted primarily of paresthesias affecting the hands and feet. Peripheral sensory neuropathy and peripheral motor neuropathy led to treatment discontinuation in 8 and 3% of patients, respectively [41]. The overall median time to PN onset was 12.4 weeks, with the onset of grade 3 PN generally observed during cycles 9 – 16. In 13 of 18 patients with grade 3 events, neuropathy symptoms resolved or lessened to grade 1 or 2 by delaying, reducing or discontinuing dosing with brentuximab vedotin [44-47], and overall, 49% of patients who experienced any grade of neuropathy had complete resolution, 31% had partial improvement and 20% had no improvement [41]. In general, a dose delay and reduction to 1.2 mg/kg i.v. q3 weeks are, therefore, recommended for the management of brentuximab vedotin-related toxicity, and in the Phase II studies, PN was generally manageable through dose delay and dose reduction to 1.2 mg/kg q3 weeks [44-47].

4.2 Neutropenia

Across the two Phase II studies, 36 (23%) patients experienced grade 3 (n = 24) or grade 4 (n = 12) neutropenia, based on reported adverse event or laboratory results [44-47]. Neutropenia appeared to be well managed with standard recommendations for hematological toxicity, including dosing delays and growth factor support. Three patients had grade 4 neutropenia that lasted for ≥ 7 days. Of the patients with neutropenia, fewer than 50% had temporally associated infections, generally of grade 1 or 2 severity. No adverse events of febrile neutropenia were reported in the Phase II studies [44-47].

4.3 Infusion reactions

Events considered to potentially represent infusion reactions occurred in 11% of patients in the Phase II pivotal studies [56]. Nearly all were of mild-to-moderate severity and occurred during the first two treatment cycles. Infusion reactions were characterized by chills (4%), nausea, dyspnea, pruritus (3% each) and cough (2%). The incidence of infusion reactions appeared to be higher in patients with persistently positive anti-brentuximab vedotin antibody titers (3 of 10 patients, 30%) relative to those with transiently positive titers (5 of 42 patients, 12%) or those who were never positive (7 of 96 patients, 7%) [56]. In Phase I studies, two cases of anaphylaxis were reported; one event resulted in treatment discontinuation and the other patient continued treatment with prophylaxis and a longer infusion time [56].

4.4 Other adverse events of interest

Other common adverse events reported in the Phase I [40,43] and Phase II studies [44-47] were fatigue, pyrexia, gastrointestinal events, dizziness and myalgia, which were predominantly of mild-to-moderate severity. Overall, infections were observed in 58% of patients in the two Phase II studies, with the most frequent events being grade 1 or 2 upper respiratory tract infections [56]; no patient discontinued treatment with brentuximab vedotin due to an infection. Rare but notable adverse events included a case of treatment-related grade 3 tumor lysis syndrome in a patient with sALCL, and a case of Stevens–Johnson syndrome in a patient receiving brentuximab vedotin and a concomitant nonsteroidal anti-inflammatory drug [56]. A fatal case of progressive multifocal leukoencephalopathy has been reported in a patient who received four chemotherapy regimens prior to receiving brentuximab vedotin [41].

5. Future directions

Based on the encouraging data from Phase II studies, brentuximab vedotin is currently being investigated in multiple disease settings in ongoing clinical studies (**Table 1**), including in patients at high risk of residual HL post-ASCT (SGN35-005, the AETHERA trial, NCT01100502), as frontline therapy for HL in combination with multiagent chemotherapy (SGN35-009, NCT01060904), as frontline therapy for sALCL in combination with multiagent chemotherapy (SGN35-011, NCT01309789), in patients with relapsed CD30-positive NHL (SGN35-012), in patients with mycosis fungoides (MF) or Sézary syndrome (SS), the most common groups of CTCL, in which expression of CD30 is variable (NCT01396070) and in patients with other CD30-positive lymphoproliferative disorders (cutaneous ALCL, MF and extensive lymphomatoid papulosis; NCT01352520). Additionally, another study is planned using brentuximab vedotin as salvage therapy prior to ASCT in patients with HL (NCT01393717).

The Phase III AETHERA trial will be of particular interest for assessing the impact on PFS of brentuximab vedotin therapy, administered 30 – 45 days post-ASCT, among HL patients who are at high risk of residual disease following transplant. An estimated 322 patients will be enrolled at 69 study sites in the US and Europe and randomized to receive best supportive care following ASCT plus either brentuximab vedotin 1.8 mg/kg q3 weeks or placebo. Furthermore, the Phase I studies investigating the addition of brentuximab vedotin at the earliest opportunity in the treatment of aggressive CD30-positive lymphomas, in combination with frontline multiagent chemotherapy, will provide indicators regarding the feasibility of such an approach with regard to improving overall patient outcomes in these conditions.

6. Expert opinion

Tumor CD30 expression is observed preferentially in patients with a subset of aggressive lymphomas that, while potentially curable with frontline multiagent chemotherapy, frequently develop recurrent disease for which current salvage therapy offers little benefit. This population of patients, together

with those who have tumors initially insensitive to frontline chemotherapy, constitutes a highly unmet medical need. In early studies, brentuximab vedotin demonstrated compelling responses, tolerability and manageable toxicity in relapsed or refractory HL and sALCL, with consistent and unprecedentedly high rates of OR and CR across Phase I and II studies [40,43-47]. This ADC, therefore, appears to offer potential for the treatment of these diseases. Delivery of MMAE to CD30-expressing tumor cells is, to the best of our knowledge, the main mechanism of action of brentuximab vedotin. Other potential mechanisms such as modulation of the immune system, CD30 signaling or tumor microenvironment bystander effects are speculative at the present time. Despite the impressive responses observed in early studies, our ability to assess the clinical benefit derived from brentuximab vedotin treatment is limited by the single-arm study designs employed and the absence of large trials of other agents in the settings of relapsed or refractory HL and sALCL, which would allow comparisons with historical data. Nevertheless, relapsed or refractory HL and sALCL are encountered rarely, and although randomized controlled trials are the preferable means for assessing the effectiveness of new therapies, single-arm pivotal studies are not unusual in orphan drug development due to small patient population size and the frequent absence of appropriate comparators [57]. Moreover, since spontaneous regression of advanced aggressive lymphomas is an extremely rare event, it is reasonable to attribute the observed regressions to a treatment effect. The high CR rates observed with brentuximab vedotin could be particularly meaningful, as durable CRs have been associated with long-term clinical benefit in HL [58]. Similar correlations have not been established in sALCL, but a large meta-analysis of NHL trials recently found that differences in CR rate strongly correlated with differences in 3-year time-to-event endpoints in aggressive lymphomas [59]. In August 2011, brentuximab vedotin was approved in the US for the treatment of HL after failure of ASCT or at least two prior multiagent chemotherapy regimens in ASCT-ineligible candidates, and for the treatment of sALCL after failure of at least one prior multiagent chemotherapy regimen.

In addition to the ongoing trials, multiple avenues remain to be explored in the development of brentuximab vedotin. A retrospective analysis from studies SG035-0001 and SG035-0002 of patients who were ineligible for or refused ASCT revealed that single-agent responses with brentuximab vedotin can be observed in this setting [60]. The activity of brentuximab vedotin in this patient group should be formally tested in randomized studies. Potential combination studies in the relapsed and refractory setting should also be considered, including the combination with pipeline agents. The optimal dose and combination regimens for the use of brentuximab vedotin in frontline and second-line settings remain to be determined. Additional work is required to further explore the differential expression of CD30 in subtypes of B-cell NHL and T-cell lymphoma, in order to identify patient populations in which such therapy may be of potential benefit [61]. Of note, some non-hematological indications such as embryonal carcinoma are known to overexpress CD30 and could be potential targets. CD30 expression in a subset of other solid tumors requires further investigation [62]. As with other targeted therapies, pharmacodynamic interactions should be carefully assessed. Pharmacodynamic data of soluble CD30 (sCD30) [63-65] from brentuximab vedotin trials are not yet available. sCD30 could contribute to identify a subset of aggressive lymphomas in which anti-CD30 treatment could be appropriate. On the other hand, excess sCD30 could theoretically constitute a mechanism of tumor drug resistance. Other potential mechanisms of tumor resistance include loss of CD30 expression and *de novo* expression of MMAE efflux pump transporters [66].

In summary, early results with brentuximab vedotin are very promising for relapsed or refractory HL and sALCL patients with few treatment options and have resulted in the recent approval of this agent (ADCETRIS) by the FDA for the treatment of patients with HL after failure of ASCT or after failure of at least two prior multiagent chemotherapy regimens in HL patients who are not ASCT candidates. ADCETRIS was also approved in the US for the treatment of patients with systemic anaplastic large-cell lymphoma after failure of at least one prior multiagent chemotherapy regimen [67]. This initial evidence of activity strongly supports an expanded development program for this agent in multiple CD30-positive indications.

Acknowledgements

This research was supported by Millennium: The Takeda Oncology Co. The author would also like to acknowledge the editorial support of Steve Hill, of FireKite, in the preparation of this review, which was funded by Millennium: The Takeda Oncology Co.

Declaration of interest

A Gualberto is an employee of Millennium: The Takeda Oncology Company that develops ADCETRIS in collaboration with Seattle Genetics. The author states no conflict of interest and has received no payment in preparation of this manuscript.

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