

# A Phase II study of SGN-30 (anti-CD30 mAb) in Hodgkin lymphoma or systemic anaplastic large cell lymphoma

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CD30 is a member of the tumour necrosis factor (TNF) receptor superfamily, which was originally found in the Reed-Sternberg cell in Hodgkin lymphoma (HL) (Durkop *et al*, 1992). Subsequent studies demonstrated that CD30 expression on normal cells was restricted to activated T- and B-lymphocytes and eosinophils (Falini *et al*, 1995; Gruss & Herrmann, 1996; Matsumoto *et al*, 2004). In addition, variable CD30 expression has been demonstrated on several lymphomas but most consistently on HL and anaplastic large cell lymphoma (ALCL) (Falini *et al*, 1995). CD30 is also expressed by embryonal carcinoma (Falini *et al*, 1995).

The function of CD30 has not been clearly defined but it has been implicated in both cell death and proliferation. Two studies have shown that monoclonal antibodies

## Summary

SGN-30, a chimeric anti-CD30 monoclonal antibody, has demonstrated potent preclinical antitumour activity in both Hodgkin lymphoma (HL) and anaplastic large cell lymphoma (ALCL). We conducted an open-label, Phase II study to determine the safety and objective response rate of SGN-30 in 79 patients with refractory/recurrent HL ( $n = 38$ ) or systemic ALCL ( $n = 41$ ). Each course of SGN-30 comprised 6 weekly intravenous infusions, followed by a 2-week treatment-free period. Patients had received a median of 3 (range 1–5) prior regimens of chemotherapy or systemic therapy. The initial 40 patients received 6 mg/kg weekly; the latter 39 patients received 12 mg/kg weekly. In the ALCL group, two patients achieved a complete response and five additional patients achieved a partial response, with response durations ranging from 27 to 1460+ d. No objective responses were observed in the HL group; however, 11 patients (29%) had stable disease (duration 62–242 days). Although adverse events were common, most were mild or moderate, and no specific pattern of adverse events was observed in either disease group. These results demonstrate that weekly administration of SGN-30 is safe, with modest clinical activity in patients with ALCL.

**Keywords:** Hodgkin lymphoma, anaplastic large cell lymphoma, monoclonal antibody, anti-CD30 antibody, anaplastic lymphoma kinase.

directed to CD30 were able to inhibit the growth of HL cells in severe combined immunodeficiency (SCID) mice in the absence of immune effector cells, suggesting a direct effect of CD30 on tumour cells (apoptosis inducing characteristics) (Wahl *et al*, 2002; Borchmann *et al*, 2003). Like other TNF-receptor superfamily members, CD30 has been shown to activate nuclear factor  $\kappa$ B (NF- $\kappa$ B), extracellular-regulated kinase (ERK), Jun N-terminal kinase (JNK), and p38 (Duckett *et al*, 1997; Harlin *et al*, 2002; Zheng *et al*, 2003).

SGN-30 is an antagonist chimeric monoclonal antibody constructed from the variable region of the anti-CD30 murine antibody AC10 and the human gamma 1 heavy chain and kappa light chain constant regions (Wahl *et al*, 2002). SGN-30

has specificity for CD30 that is unique from other anti-CD30 antibodies, has demonstrated antitumour activity in both *in vitro* and *in vivo* HL and ALCL cell lines and disseminated and localized xenograft models, (Wahl *et al*, 2002) and has shown a cytotoxic synergism with different chemotherapy agents *in vitro* including bleomycin, etoposide, and cytarabine (Cervený *et al*, 2005).

A single-dose, Phase I, dose-escalation clinical study in patients with CD30-positive (CD30<sup>+</sup>) malignancies was conducted in which SGN-30 was well tolerated, with no Grade 3 non-haematological or haematological toxicities at doses up to 15 mg/kg, and preliminary evidence of activity was observed (Bartlett *et al*, 2002). In addition, a Phase I multi-dose, dose-escalation study was conducted in patients with refractory, relapsed CD30<sup>+</sup> haematological malignancies. Again, 6 weekly doses (one course, up to 12 mg/kg) of SGN-30 were well tolerated; nausea, fatigue, and fever were attributed to study treatment, but no dose-limiting toxicities were observed, and the maximal tolerated dose was not reached. Antitumour activity was observed: one patient with systemic ALCL achieved complete response, and six patients (four with HL) achieved stable disease with durations ranging from 6 to 16 months. The 6 weekly infusions resulted in approximately 2- to 3-fold accumulation in serum exposure to SGN-30 that was consistent across the dose range (Bartlett *et al*, 2008).

We undertook this open-label, Phase II study to determine the safety and objective response rate of SGN-30 in patients with refractory or recurrent HL and systemic ALCL.

## Methods

### Patients

Eligible patients were at least 18 years of age and had histologically-confirmed CD30<sup>+</sup> refractory or recurrent HL or systemic ALCL (tissue availability for central review was required for participation in the trial). Patients with primary cutaneous ALCL with no systemic involvement were excluded from the trial. Documentation of anaplastic lymphoma kinase (ALK) status was required before enrollment for patients with ALCL. Patients were required to have measurable disease on physical examination or radiological evaluation, had failed systemic chemotherapy either as initial therapy for advanced disease or as salvage therapy after initial radiotherapy for early stage disease, and had refused, were ineligible for, or had failed high-dose chemotherapy with autologous stem cell rescue. Patients who received more than four previous therapies were excluded, as were patients who had received a prior allogeneic stem cell transplant.

All patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, a life expectancy of at least 3 months, and be a minimum of 4 weeks from prior chemotherapy, radiotherapy, or investigational agent (6 weeks for mustard agents, melphalan, or BCNU [carmustine]). Required laboratory values at study entry were

as follows: absolute neutrophil count (ANC)  $\geq 1 \times 10^9/l$ ; platelet count  $\geq 50 \times 10^9/l$ ; serum bilirubin  $\leq 1.5$  times upper limit of normal (ULN); serum creatinine  $\leq 1.5$  times ULN; and blood urea nitrogen (BUN)  $\leq 1.5$  times ULN. Support was allowed with growth factors and/or transfusions. Females of childbearing potential must have had a negative beta human chorionic gonadotropin ( $\beta$ -HCG) pregnancy test result within 3 d of enrollment, and all patients agreed to use an effective contraceptive method during the course of the study.

Patients were excluded if they had had a known hypersensitivity to recombinant proteins or any excipient contained in the drug formulation; had a history of other malignancies during the past 5 years (with the exception of basal or squamous cell skin cancer or cervical carcinoma *in situ*); had a known systemic viral, bacterial, or systemic fungal infection, or were known to be human immunodeficiency virus, hepatitis B, or hepatitis C positive; had symptomatic cardiac disease; had known symptomatic brain involvement requiring treatment; had any serious underlying medical condition that would impair their ability to receive or tolerate the planned treatment; or had dementia or altered mental status that would preclude understanding and rendering of informed consent.

The study was conducted according to the Declaration of Helsinki and the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice. Approvals from appropriate research ethics committees were obtained from each participating study centre. All patients provided written informed consent before participating.

### Study design and schedule

This was an open-label, Phase II study to define the safety profile and assess the antitumour activity of SGN-30 in two study groups, patients with refractory or recurrent HL and patients with refractory or recurrent systemic ALCL. The study was conducted for 2 years at 27 study centres in the United States (17) and Europe (10).

Each course of SGN-30 comprised 6 weekly intravenous (IV) infusions, followed by a 2-week treatment-free period; patients were evaluated for response at week 8. Additional courses were determined using the following criteria: patients who experienced Grade 3 or 4 haematological or non-haematological toxicity determined to be possibly, probably, or definitely related to study drug were not permitted to receive additional SGN-30; patients with progressive disease at the end of the first course or at any time during treatment were removed from the study; patients with a complete response (CR), or partial response (PR) at the end of the first course received additional courses after documentation of antitumour activity (patients were allowed to receive up to four courses of SGN-30); and patients with decrease in tumour volume and who had a clinical benefit in the opinion of the investigator were also allowed to receive additional courses of SGN-30. Response evaluations were centrally reviewed.

The first 40 patients enrolled in the study (15 in the HL group and 25 in the ALCL group) received SGN-30 at a dose of 6 mg/kg weekly. In an effort to increase the objective response rates and after an interim analysis of the safety data and the review of the response data from the previous Phase I study, the dose of SGN-30 was increased to 12 mg/kg weekly for the remaining patients.

### *Drug formulation and administration*

SGN-30 was supplied by Seattle Genetics, Inc. (Seattle, WA, USA) as 100 mg (10 mg/ml) of sterile, colourless, slightly opalescent, preservative-free, monoclonal antibody in single-use Type I borosilicate glass vials. Study drug was administered at an initial rate of 100 mg/h for the first 30 min; in the absence of hypersensitivity or infusion reactions, the remainder of the dose was administered over the next 90 min for a total infusion time of 2 h. Pre-medication was not routinely administered during this study, but was allowed at the discretion of the investigator.

### *Study assessments*

Baseline assessments for all patients included: medical history and physical examination, haematology analyses, chemistry panel, urinalysis, human anti-chimeric antibody (HACA), tumour assessment by radiological images [computed tomography (CT) or magnetic resonance imaging (MRI)], and bone marrow biopsy.

To evaluate safety, patients were monitored throughout the study by physical examination, laboratory analysis, immunogenicity testing, and assessment of adverse events (AEs). Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0 ([http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/ctcae3.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf)). Similar follow-up assessments were performed 2–4 weeks post-treatment. Only treatment-emergent AEs, defined as events with onset on or after the first dose, were of interest.

Assessment of response (the primary endpoint of the study) was performed after every 8-week course of treatment using the same radiological imaging modality used at the baseline evaluation. Patients whose disease had not progressed at the end of the study were evaluated every 3 months until disease progression. Antitumour responses were defined using the Cotswolds criteria for patients with HL (Lister *et al*, 1989) and the International Workshop Standardized Response Criteria for non-Hodgkin lymphoma patients (Cheson *et al*, 1999).

### *Human anti-chimeric antibody (HACA) response*

Serum samples were collected at baseline, prior to the first dose of every course, end of each course, and follow-up assessments. Sera were frozen at  $-20^{\circ}\text{C}$  or below and shipped

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for analysis. HACA were measured by a validated enzyme-linked immunosorbent assay. Briefly, microtitre plates, pre-coated with SGN-30, were incubated with dilutions of serum samples, and bound anti-SGN-30 antibodies were detected with a biotinylated SGN-30 conjugate, Streptavidin-conjugated horseradish peroxidase served as a colorimetric indicator. HACA titres were assessed for positive samples based on dilutions with signals above a cut-off point determined from negative control values.

### *Statistical analysis*

The primary objectives of this Phase II study were to determine the antitumour activity and the safety of SGN-30 in patients with relapsed/refractory, CD30<sup>+</sup>, HL and ALCL lymphomas. Safety analyses were performed on all patients who received at least one dose of SGN-30. Analyses of antitumour activity included all patients who received at least one dose of SGN-30 (intent-to-treat population) and had at least one assessment of tumour status after baseline or had clinical evidence of progression prior to the assessment of tumour status; patients were classified according to the best overall response: CR, PR, stable disease, or progressive disease. Descriptive statistics were used to present the safety and antitumour activity results in each group (HL and ALCL patients), and in each SGN-30 dose group (6 and 12 mg/kg weekly). All statistical summaries and individual data listings were done using the statistical software SAS, version 9.1 (SAS Institute Inc, Cary, NC, USA). Additional parameters of antitumour activity included duration of tumour response and progression-free survival.

## Results

### *Patient characteristics*

Eighty-two patients were enrolled in the study; of these, 79 patients (38 in the HL group and 41 in the ALCL group) received at least one dose of SGN-30 and were evaluable (Fig 1). Patient characteristics, by disease diagnosis and dose level, are shown in Table I. Prior to study entry, patients had been heavily pretreated; most [65/79 (82.3%)] had failed more than 1 prior chemotherapy or systemic therapy, and many [34/79 (43.0%)] had received prior stem cell/bone marrow transplantation. Of the 41 ALCL patients, 35 (85%) were ALK-negative, four patients were ALK-positive, and data were unavailable for two patients.

### *Drug Delivery*

Of the 38 patients in the HL group, all but one (who discontinued due to hypersensitivity reaction on Day 22) received at least one full course (six doses) of SGN-30 (15 patients in the 6-mg/kg group and 22 in the 12-mg/kg group; Fig 1). One patient in the 12-mg/kg group received three courses; no other HL patient received more than one course.

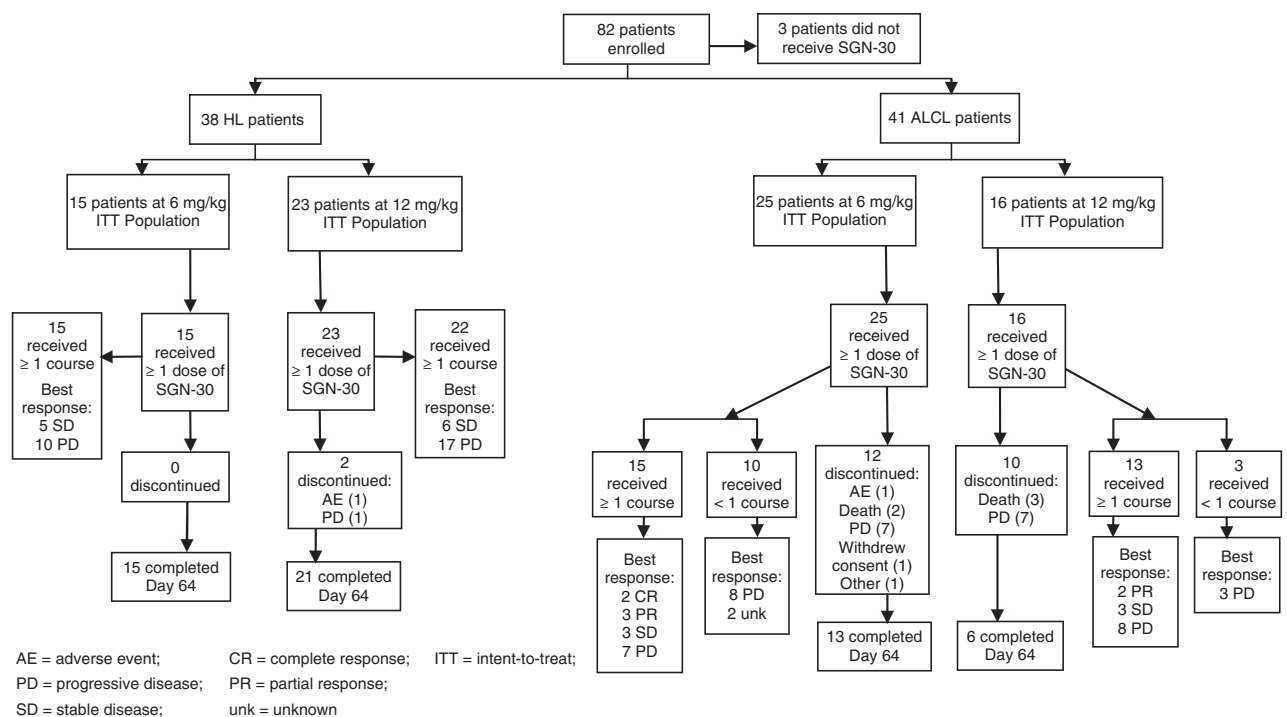


Fig 1. CONSORT Diagram.

Twenty-eight of 41 patients in the ALCL group received at least one full course (six doses) of therapy (15 in the 6-mg/kg dose group and 13 in the 12-mg/kg dose group; Fig 1); 10 patients received more than one course (five in the 6-mg/kg dose group and five in the 12-mg/kg dose group). Thirteen patients were not able to receive a complete course of SGN-30: 11 due to disease progression (eight in the 6-mg/kg dose group and three in the 12-mg/kg dose group), and one each due to AE (blood infection) and withdrawal of consent (both patients in the 6-mg/kg group).

### Antitumour Activity

No patients in the HL group achieved an objective response. However, 28.9% of these patients had stable disease (five patients in the 6-mg/kg dose cohort and six patients in the 12-mg/kg dose cohort), with a median duration of stable disease of 119+ d (4+ months; range 62 to 242+ d).

The objective response rate (CR + PR) in the intent-to-treat population of ALCL patients was 17.1% (25.0% for the group of 28 ALCL patients that received at least one course of therapy; Fig 1): two ALCL patients in the 6-mg/kg dose group achieved a CR; and five ALCL patients (three in the 6-mg/kg group and two in the 12-mg/kg group) achieved a PR during the study (Table II). In addition, 14.6% of the patients with ALCL had stable disease. All responders (CR or PR) were ALK-negative. Thus, the clinical benefit of SGN-30, as assessed by maintaining stable disease or achieving a response to therapy, was demonstrated in 28.9%

of HL patients and 31.7% of ALCL patients in the ITT population.

For the two ALCL patients who achieved CRs, the duration of response was 172+ and 1460+ d respectively (Table II). Both patients who achieved CR were heavily pretreated: one patient had received three different chemotherapy regimens and was ineligible for autologous stem cell transplant due to chemoresistance; the other patient had failed front-line and consolidation therapy. The median duration of response for those ALCL patients who achieved PR was 100 d (range 27–217 d).

### Safety

SGN-30 was well tolerated with no treatment-related deaths. As shown in Table III, adverse events were reported in 93.7% of the patients enrolled in the trial. The most common adverse events were fatigue (31.6%), nausea (20.3%), pyrexia (20.3%), and headache (17.7%). Twenty-nine patients (36.7%) experienced a Grade 3 or 4 adverse event during the study; incidence was greater in the ALCL group [23 patients (56.1%)] than in the HL group [six patients (15.8%)].

A total of 44 serious adverse events (SAEs) occurred in 23 patients during the study. Most SAEs were considered unrelated or unlikely to be related to the study drug. Of SAEs that were considered to be possibly related to SGN-30, three occurred in the HL group: one patient in the 12-mg/kg group had pre-syncope, and two patients in the 12-mg/kg group had unexpected tumour progression. At the first restaging

Table I. Baseline demographics and disease characteristics.

	HL Patients SGN-30 dose level		ALCL Patients SGN-30 dose level		All Patients (N = 79)
	6 mg/kg (n = 15)	12 mg/kg (n = 23)	6 mg/kg (n = 25)	12 mg/kg (n = 16)	
Age, years					
Median	34.0	36.0	57.0	55.0	44.0
Range	20–65	21–60	23–78	29–82	20–82
Male, number (%)	6 (40.0%)	10 (43.5%)	14 (56.0%)	11 (68.8%)	41 (51.9%)
Race, number (%)					
Caucasian	11 (73.3%)	17 (73.9%)	21 (84.0%)	15 (93.8%)	64 (81.0%)
Black	2 (13.3%)	3 (13.0%)	2 (8.0%)	1 (6.3%)	8 (10.1%)
Asian/Pacific Islander	0	0	1 (4.0%)	0	1 (1.3%)
Hispanic	2 (13.3%)	2 (8.7%)	0	0	4 (5.1%)
Other	0	1 (4.3%)	1 (4.0%)	0	2 (2.5%)
ECOG Performance Status, number (%)*					
0	9 (81.8%)	14 (77.8%)	11 (47.8%)	6 (37.5%)	40 (58.8%)
1	2 (18.2%)	3 (16.7%)	8 (34.8%)	5 (31.3%)	18 (26.5%)
2	0	1 (5.6%)	4 (17.4%)	5 (31.3%)	10 (14.7%)
Karnofsky Performance Status, number (%)*					
100	0	2 (40.0%)	1 (50.0%)	0	3 (27.3%)
90	3 (75.0%)	2 (40.0%)	1 (50.0%)	0	6 (54.5%)
80	0	1 (20.0%)	0	0	1 (9.1%)
70	1 (25.0%)	0	0	0	1 (9.1%)
Years from initial diagnosis (mean [median])	3.79 (3.40)	4.36 (2.60)	2.18 (1.10)	3.24 (2.55)	3.33 (2.50)
Received prior autologous BMT, number (%)	10 (66.7%)	16 (69.5%)	4 (16.0%)	4 (25.0%)	34 (43.0%)
Received prior radiotherapy, number (%)	10 (66.7%)	17 (73.9%)	13 (52.0%)	9 (56.3%)	49 (62.0%)
Number (%) of prior regimens of chemotherapy/systemic therapy					
0	0	0	0	1 (6.3%)†	1 (1.3%)
1	1 (6.7%)	2 (8.7%)	6 (24.0%)	4 (25.0%)	13 (16.5%)
2	0	2 (8.7%)	6 (24.0%)	4 (25.0%)	12 (15.2%)
3	5 (33.3%)	9 (39.1%)	8 (32.0%)	3 (18.8%)	25 (31.6%)
4	9 (60.0%)	9 (39.1%)	4 (16.0%)	3 (18.8%)	25 (31.6%)
5	0	1 (4.3%)	1 (4.0%)	1 (6.3%)	3 (3.8%)

\*Patients were assessed at baseline for either ECOG (Eastern Cooperative Oncology Group) or Karnofsky score, but not both; denominators include only the relevant patients.

†One ALCL patient in the 12-mg/kg group was granted a waiver for not meeting the inclusion criterion of receiving at least one prior systemic therapy.

BMT, bone marrow transplantation.

Table II. Best clinical response, intent-to-treat population.

	HL Patients SGN-30 dose level			ALCL Patients SGN-30 dose level		
	6 mg/kg (n = 15)	12 mg/kg (n = 23)	Total (n = 38)	6 mg/kg (n = 25)	12 mg/kg (n = 16)	Total (n = 41)
Complete response (CR, n [%])	0	0	0	2 (8.0%)	0 (0.0%)	2 (4.9%)
Duration CR (median days)	NA	NA	NA	172+, 1460+	NA	NA
Partial response (PR, n [%])	0	0	0	3 (12.0%)	2 (12.5%)	5 (12.2%)
Duration PR (median days)	NA	NA	NA	53	147.5	NA
Objective response (CR or PR), n (%)	0	0	0	5 (20.0%)	2 (12.5%)	7 (17.1%)
Stable disease (SD, n [%])	5 (33.3%)	6 (26.1%)	11 (28.9%)	3 (12.0%)	3 (18.8%)	6 (14.6%)
Clinical benefit (CR + PR + SD, n [%])	5 (33.3%)	6 (26.1%)	11 (28.9%)	8 (32.0%)	5 (31.2%)	13 (31.7%)
Progressive disease, n (%)	10 (66.7%)	17 (73.9%)	27 (71.1%)	15 (60.0%)	11 (68.8%)	26 (63.4%)
Unknown, n (%)	0	0	0	2 (8.0%)	0	2 (4.9%)

NA, not applicable.

Table III. Summary of adverse events.

Number (%)	HL Patients SGN-30 dose level		ALCL Patients SGN-30 dose level		Total (N = 79)
	6 mg/kg (n = 15)	12 mg/kg (n = 23)	6 mg/kg (n = 25)	12 mg/kg (n = 16)	
Any adverse event	12 (80.0%)	23 (100.0%)	23 (92.0%)	16 (100.0%)	74 (93.7%)
Most common AE					
Fatigue	6 (40.0%)	8 (34.8%)	8 (32.0%)	3 (18.8%)	25 (31.6%)
Nausea	1 (6.7%)	8 (34.8%)	5 (20.0%)	2 (12.5%)	16 (20.3%)
Pyrexia	0	7 (30.4%)	5 (20.0%)	4 (25.0%)	16 (20.3%)
Headache	0	7 (30.4%)	5 (20.0%)	2 (12.5%)	14 (17.7%)
Any CTC Grade 3 or Grade 4 AE	1 (6.7%)	5 (21.7%)	12 (48.0%)	11 (68.8%)	29 (36.7%)
Dyspnea	0	1 (4.3%)	1 (4.0%)	2 (12.5%)	4 (5.1%)
Anaemia	0	1 (4.3%)	2 (8.0%)	0	3 (3.8%)
Cardiac failure	0	0	1 (4.0%)	2 (12.5%)	3 (3.8%)
Hypersensitivity event	1 (6.7%)	1 (4.3%)	1 (4.0%)	0	3 (3.8%)
Serious adverse event	0	6 (26.1%)	9 (36.0%)	8 (50.0%)	23 (29.1%)
Treatment-related SAE	0	3 (13.0%)	2 (8.0%)	0	5 (6.3%)
AE leading to discontinuation	0	1 (4.3%)	1 (4.0%)	0	2 (2.5%)
Deaths*	0	0	5 (32.0%)	2 (12.5%)	7 (8.9%)

\*Six of the seven deaths were due to the primary malignancy or progression of disease; one patient had an infection leading to multisystem organ failure. No deaths were considered by the investigator to be related to study drug.

AE, adverse event; SAE, serious adverse event; CTC, common toxicity criteria.

assessment, the latter two patients were observed to have progressed more rapidly than expected in the absence of study treatment, in the investigator's opinion. One patient had nodular sclerosing HL with multiple retroperitoneal nodes and a paraspinal soft tissue mass at baseline; following one course of SGN-30, a positron emission tomography/CT scan revealed an increase in the paraspinal soft tissue mass from 4.6 × 1.7 cm at pretreatment to 6.1 × 2.0 cm, but minimal changes were observed in other index lesions; the patient was removed from the study and radiotherapy was recommended. The second patient had nodular sclerosing HL at baseline; after one course of SGN-30, the axillary nodes, which were non-confluent and 1–2 cm in diameter at pretreatment, were confluent and had increased to 4 × 6 cm; additionally, CT scans and clinical measurements also revealed an increase in a left subpectoral mass from 3 × 3.5 cm at pretreatment to 4.4 × 5.9 cm. A rigorous retrospective review of their medical histories showed no unusual findings in these patients.

Two SAEs considered possibly related to SGN-30 occurred in the ALCL group. One patient (with cutaneous involvement) in the 6-mg/kg group developed a diffuse erythematous rash with severe itching after two doses of SGN-30; a biopsy was consistent with cutaneous ALCL; following resolution of the rash (within 1 week), SGN-30 was restarted; midway through the second course of therapy, the nodules had almost resolved, and a CT scan revealed resolution of pre-existing pelvic lymph nodes; the patient completed four courses. A second ALCL patient in the 6-mg/kg group had lymphopenia.

Three patients experienced hypersensitivity or allergic reactions: a patient in the 6-mg/kg HL group had treatment interrupted on Day 1, but completed the study treatment with

no additional hypersensitivity events; a patient in the 12-mg/kg HL group (previously described) was discontinued on Day 22 due to the event; and a patient in the 6-mg/kg ALCL group experienced increased itching during the Day-8 administration, but completed the study with no further hypersensitivity events and achieved a partial response.

Seven patients died during the study, between the initial dose and within 4 weeks after the last dose of SGN-30. Most deaths were the result of the primary malignancy or progression of disease, and none were considered related to the study drug.

#### Human anti-chimeric antibody (HACA) response

A total of 193 samples were analysed. Although none of the samples collected after the administration of at least one dose of SGN-30 showed any presence of HACA specific to SGN-30, it is possible that high serum concentrations of SGN-30 may have reduced assay sensitivity. Two samples collected before any exposure to SGN-30 were positive; these positive results are considered to be due to cross-reactivity of the assay.

#### Discussion

While more than 80% of patients with stage I or II HL are cured with combination chemotherapy followed by involved field radiation therapy, the cure rate for patients with stage III HL, while not as high, ranges from 70% to 80% and is above 50% for those patients with stage IV disease (Ansell & Armitage, 2006). Prognosis for other CD30<sup>+</sup> lymphomas, particularly systemic ALCL, is more variable and depends on

features such as the expression of the anaplastic lymphoma kinase-1 protein (ALK-1); the 5-year overall survival for those patients with ALK-positive ALCL treated with anthracycline-containing regimens is 70–80%, while it varies between 30% and 45% for those patients with ALK-1 negative-ALCL (Falini *et al*, 1999; Gascoyne *et al*, 1999). Patients who relapse after initial therapy, particularly those with HL, generally are treated with salvage chemotherapy followed by high-dose chemotherapy with autologous stem cell rescue; the cure rate for these latter patients is approximately 50% if such patients respond to salvage therapy, and is somewhat lower among patients who relapse in the first 12 months after initial treatment and higher for those patients who relapse later. Few treatment options are available for patients with refractory or recurrent CD30<sup>+</sup> haematological malignancies, especially after failure of autologous or allogeneic bone marrow transplant, which represents an unmet medical need. Thus, this study was designed to explore the safety and antitumour activity of SGN-30, an anti-CD30 monoclonal antibody, in heavily pretreated patients with HL and ALCL.

Bispecific antibodies, (Hartmann *et al*, 1998; Borchmann *et al*, 2002) immunotoxins, (Falini *et al*, 1992; Schnell *et al*, 2002) and radioimmunoconjugates (Schnell *et al*, 2005) targeting CD30<sup>+</sup> relapsed/refractory lymphomas have been evaluated in clinical trials with modest results. More recently, Ansell *et al* (2007) reported safety and efficacy of the human, naked anti-CD30 antibody MDX-060 in patients with relapsed/refractory CD30<sup>+</sup> lymphomas (63 HL patients, seven ALCL patients, and two T-cell lymphomas); in that trial, MDX-060 was well tolerated with minimal toxicity and the maximal tolerated dose was not reached. Antitumour activity in that trial included four complete responses (two in the HL group and two in the ALCL group), and two partial responses (both in the HL group). However, four of the responding HL patients received concomitant steroids, and although these patients were considered by the investigators to be refractory to previous corticosteroid therapy, its use may have contributed to the clinical response observed. Twenty-five patients in the study had stable disease, including five patients who remained in remission for more than a year. We have recently reported the results of the Phase I trial of SGN-30 (Bartlett *et al*, 2008) in which the chimeric monoclonal antibody was well tolerated with minimal toxicity and the maximal tolerated dose was not reached. Although antitumour activity was not an objective of that trial, one of three ALCL patients achieved complete response, and four of the 21 HL patients had stable disease with durations ranging from 6 to 16 months.

As in previous trials targeting CD30 (including the Phase I trial of SGN-30), in the current Phase II study of SGN-30, clinically meaningful antitumour activity was observed in heavily pretreated systemic ALCL patients, indicating biological activity of SGN-30. In this trial, the objective response rate was 17%, and it was 25% for the 28 ALCL patients who received at least one full course of SGN-30, which is similar to

the limited Phase I/II experience with MDX-060 reported by Ansell *et al* (2007). Additionally, 15% of the ALCL patients in the current Phase II study had stable disease, which may represent clinical benefit. As expected, the majority of the ALCL patients enrolled in the trial were ALK-1 negative (85%). All responses were seen in the ALK-1 negative patients. Thus, the evidence of antitumour activity of SGN-30 in ALCL patients (especially in the poor prognosis group) make the use of this agent in combination with other active standard therapies (particularly chemotherapy) an attractive option for ongoing salvage and front-line studies.

No objective responses to SGN-30 were observed in HL, similar to the modest activity of other anti-CD30 monoclonal antibodies such as MDX-060. As in previous clinical trials, however, a meaningful number of HL patients (29%) had stable disease. This modest antitumour activity of SGN-30 against HL may reflect the fact that CD30 expression in HL is primarily restricted to Reed-Sternberg cells, which form a minority of the tumour cells compared with the homogeneous expression of CD30 in the ALCL tumour cells. Thus, the bulk of HL tumour masses do not display the target antigen; it may be advantageous to combine SGN-30 with other agents (such as chemotherapy) to increase antitumour efficacy. *In vitro* data have demonstrated the synergy of SGN-30 with a number of chemotherapy agents, supporting this approach. Phase I/II trials of SGN-30 with combination therapy and alternative approaches such as antibody-drug conjugates directed against the CD30 antigen [SGN-35, cAC10 conjugated to an auristatin (monomethyl auristatin E)] are ongoing in heavily pretreated patients with CD30<sup>+</sup> haematological malignancies.

After an interim analysis of the safety data and a review of the response data from the previous Phase I study, the dose of SGN-30 in this study was increased to 12 mg/kg weekly. Although the number of patients in each group is limited, the data do not suggest a relationship between antitumour activity or safety and dose level in either HL or ALCL patients.

The collective results of this Phase II study demonstrate that SGN-30 administered to patients with relapsed or refractory HL and systemic ALCL was well tolerated, with hypersensitivity or allergic reactions observed in only three of 79 patients (4%). The acceptable safety profile of SGN-30 and the modest observed antitumour activity make the use of this agent in combination with other therapies an attractive option for future studies, particularly in the setting of ALCL.

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