Phase I Multidose-Escalation Study of the Anti-CD19 Maytansinoid Immunoconjugate SAR3419 Administered by Intravenous Infusion Every 3 Weeks to Patients With Relapsed/Refractory B-Cell Lymphoma

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ABSTRACT

Purpose

We determine the maximum-tolerated dose (MTD), pharmacokinetics, safety, and preliminary efficacy of SAR3419, an antibody-drug conjugate targeting CD19, in a first-in-man phase I clinical trial in patients with relapsed lymphoma.

Patients and Methods

Patients with relapsed CD19+ B-cell lymphoma were treated with escalating doses of SAR3419 given by intravenous infusion once every 21 days.

Results

Thirty-nine patients were treated on seven dose levels ranging from 10 to 270 mg/m². The median number of prior treatment regimens was four (range, 1 to 9), and 11 patients had prior autologous or allogeneic stem-cell transplantation. The dose-limiting toxicities were reversible severe blurred vision associated with microcystic epithelial corneal changes reported in six patients and neuropathy in one patient. The MTD was 160 mg/m² once every 21 days. Hematologic and hepatic toxicities were predominantly grade 1 or 2 in severity. A total of 35 patients have completed at least two cycles of treatment and were evaluable for tumor response. Twenty-six patients (74%) demonstrated reduction in their tumor size; six of those patients achieved partial or complete remissions. Seven (47%) of 15 patients with rituximab-refractory disease demonstrated reduction in their tumor sizes. The pharmacokinetic profile of SAR3419 is characterized by linear kinetics, low clearance from 0.2 to 0.6 L/d/m², and an elimination half-life in the range of 3 to 7 days.

Conclusion

Using an every 3-week-schedule of SAR3419 for six cycles, the MTD is 160 mg/m². SAR3419 can be safely administered to patients with relapsed B-cell lymphoma and demonstrates promising clinical activity, including patients who were refractory to rituximab.

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INTRODUCTION

Antibody-drug conjugates (ADCs) provide an opportunity to selectively deliver cytotoxic therapy to cancer cells and, therefore, can improve the therapeutic efficacy of the naked antibody while decreasing the toxicity of systemically administered cytotoxic therapy.^{1,2} In contrast with naked antibodies, an ideal ADC target should be internalized to allow delivery of the cytotoxic drug inside the tumor cells.^{1,3}

CD19, a transmembrane glycoprotein of the Ig superfamily, is expressed by normal and malignant B lymphocytes from the early pre-B-cell differentiation until terminal differentiation into plasma

cells.^{4,5} CD19 is an attractive target for monoclonal antibody therapy because it has the potential to provide therapeutic benefit to a wider range of B-cell malignancies compared with CD20 and may also provide a therapeutic advantage by depleting early pathogenic B-cell precursors that may escape from CD20-targeted agents.⁴ Further, unlike CD20, CD19 is internalized efficiently, making it an attractive target for ADC therapy.

SAR3419 (huB4-DM4) is a humanized IgG1 anti-CD19 monoclonal antibody.⁶ huB4 is conjugated through a disulfide linker to the potent cytotoxic maytansinoid derivative drug DM4 (Fig 1 A).^{6,8} On average, about 3.5 DM4 molecules are linked to each antibody. DM4 is a thiol-containing

Fig 1. Structure and mechanism of action of SAR3419. (A) Schematic representation of structure. (B) Target cell activation of SAR3419, based on Erickson et al.⁷

derivative of maytansine, a potent antimetabolic agent that inhibits tubulin polymerization and microtubule assembly, inducing cell cycle arrest in the G2/M phase of the mitotic cycle.⁹⁻¹¹ In preclinical models, SAR3419 was found to be more active than both the unconjugated antibody alone and free DM4, demonstrating the added value of the immunoconjugation.⁸ huB4 monoclonal antibody has a limited antibody-dependent cell cytotoxicity and no complement-dependent cytotoxicity activity.⁸ After binding to the cell-surface antigen, the complex immunoconjugate-antigen is internalized and undergoes lysosomal degradation of the conjugate, generating the intermediate unstable metabolite Lysine-SPDB-DM4 (Fig 1B). Lysine-SPDB-DM4 undergoes additional intracellular processing through reduction of the disulfide bond to produce DM4 and subsequent S-methylation to produce S-methyl-DM4, stable and potent, and is shown to be the largest fraction of the intracellular metabolite mixture.¹² Furthermore, preclinical and toxicology studies using SAR3419 suggested promising antitumor activity against human B-cell lymphoma models and acceptable safety profile in animals. On the basis of these preclinical studies, we conducted a phase I clinical trial of SAR3419 in patients with relapsed CD19+ B-cell lymphoma.

PATIENTS AND METHODS

Study Population

Adult patients with refractory or relapsed B-cell non-Hodgkin's lymphoma (NHL) expressing the CD19 antigen were enrolled onto this study. Other main criteria for eligibility included: Eastern Cooperative Oncology Group performance score ≤ 2 , absolute neutrophil count $\geq 1,500/\mu\text{L}$, and

platelets $\geq 100,000/\mu\text{L}$; adequate renal and liver function; measurable disease; no chemotherapy or radiotherapy within 4 weeks before enrollment and no radioimmunotherapy within 12 weeks before enrollment. There was no limit on the number of prior regimens, and patients with prior autologous and allogeneic stem-cell transplantation were eligible. However, patients with Burkitt's lymphoma, lymphoblastic lymphoma, chronic lymphocytic leukemia, CNS lymphoma, known HIV infection or active viral hepatitis were not eligible for inclusion. Each site's institutional review board approved the study. Each patient provided signed informed consent before enrollment.

Study Design

This was a phase 1, open-label, dose-escalation study of SAR3419 as a single agent, administered intravenously on a classical every-3-week schedule for up to six cycles (NCT00539682), which could deliver enough safety data in the first-in-human study. The starting dose was based on the results of toxicology studies in rodent and nonrodent species and defined as the dose below the Highest Non Severely Toxic Dose because of late neurotoxicity in monkeys. The starting dose for the phase 1 study was 10 mg/m^2 . The dose-escalation schema was guided by the safety evaluation during the first 21-day cycle (cycle 1). A modified accelerated dose-escalation schema was used to guide dose escalation. One patient was enrolled onto the first dose level, then, at least three patients were enrolled onto each subsequent dose level. According to the escalation plan, the dose of SAR3419 would be doubled in each successive cohort of patients until grade ≥ 2 drug-related toxicities (graded by National Cancer Institute Common Toxicity Criteria, version 3.0) were observed. Doses were then to be increased by 30% in successive cohorts of three to six patients. Dose escalation was continued until two or more patients experienced a dose-limiting toxicity (DLT) and this dose cohort was considered the maximum administered dose. The maximum-tolerated dose (MTD) was defined as the dose one level below the maximum administered dose. Once the MTD was determined, this dose cohort was expanded to 16 additional patients to further explore the safety profile and preliminary activity of SAR3419.

DLTs were defined as any related grade 3 or 4 nonhematologic toxicity, with the exception of nausea or vomiting that was responsive to antiemetic therapy and infusion-related hypersensitivity reactions. The DLTs included grade 4 neutropenia or grade 4 thrombocytopenia lasting more than 7 days,

Table 1. Patient Characteristics

Characteristic	No. of Patients	%
Registered	39	
Completed at least one cycle, evaluable for safety	38	
Age, years		
Median	66	
Range	41-80	
Male-to-female ratio		
Male	26	
Female	13	
Histology		
Follicular lymphoma	17	44
Small lymphocytic lymphoma	10	25
Diffuse large B-cell lymphoma	5	13
Mantle cell lymphoma	5	13
Marginal zone lymphoma	2	5
Stage III or IV at study entry	38	97
No. of prior regimens		
Median	4	
Range	1-9	
Patients with prior rituximab therapy	39	100
Patients with rituximab-resistant disease	15	38
Prior stem-cell transplantation	11	28
Autologous	9	24
Allogeneic	2	5

Table 2. No. of Cycles Administered to Patients Treated by Dose Level

Total No. of Cycles per Patient	10 mg/m ² (n = 1)	20 mg/m ² (n = 3)	40 mg/m ² (n = 3)	80 mg/m ² (n = 3)	160 mg/m ² (n = 20)	208 mg/m ² (n = 7)	270 mg/m ² (n = 2)
1	0	0	1	0	3	0	0
2	1	1	0	0	6	3	0
3	0	0	0	0	1	0	0
4	0	0	1	1	3	0	1
5	0	0	0	0	0	0	1
6	0	2	1	2	7	4	0

re-treatment delay of more than 2 weeks because of delayed recovery from toxicity related to SAR3419 (except for alopecia). Although dose escalation was primarily based on the incidence of DLTs during cycle 1, toxicities that met the criteria for DLTs and were observed during cycle 2 or subsequent cycles were also taken into consideration for the dose definition.

Evaluations

Before the initiation of therapy, all patients underwent a physical exam, ECG, complete blood cell count, and serum chemistry tests. CD19 testing, either by flow cytometry analysis or immunohistochemistry, was also performed before treatment initiation by each site. Computed tomography (CT) and positron emission tomography (PET) scans were performed at baseline and then repeated every two cycles for tumor response assessment using international working group criteria.¹³ The revised response criteria were used for diffuse large B-cell lymphoma to incorporate PET scan assessment of complete remissions.¹⁴ After the occurrence of severe blurred vision in one patient, the protocol was revised to include ophthalmic monitoring at baseline and weekly in case of ocular events higher than grade 1 during the study treatment period.

Pharmacokinetics

During cycle 1, peripheral blood samples were obtained before infusion, at the end of the infusion, and 4 hours after infusion, and once per day on days 2, 3, 5, 15, and 21. For all subsequent cycles, blood samples were collected only on day 1 and day 21. Plasma concentrations of the immunoconjugate (huB4-DM4 containing at least one DM4 molecule per antibody molecule) were determined using an enzyme-linked immunosorbent assay method with a limit of quantitation of 40 ng/mL. Free DM4 and S-Methyl-DM4 were measured using a liquid chromatography-mass spectrometry method with a limit of quantitation of 5 ng/mL. For each patient, plasma concentrations of SAR3419 were plotted versus time and studied with a noncompartmental analysis technique. Peak concentration, area under the concentration curve, terminal half-life, volume of distribution, and plasma clearance were calculated for each analyte. The potential immunogenicity of SAR3419 was evaluated with enzyme-linked immunosorbent assay methods for detecting human anti-SAR3419 and anti-DM4 antibodies in plasma. Peripheral blood samples were collected before the first infusion of SAR3419 and at the end of each cycle, and one additional sample was collected on day 42 of the last cycle when possible.

Statistical Analysis

Statistical analysis was performed on patients receiving at least one dose of SAR3419. Descriptive statistics and listings were used to present the safety data, the data related to the antilymphoma activity of SAR3419, and pharmacokinetic parameters.

RESULTS

Patient Characteristics

A total of 39 patients (median age, 66 years; range, 41 to 80 years) with refractory or relapsed B-cell NHL were enrolled and treated. Thirty-eight patients (97%) had stage III or IV disease at study entry. The two most frequent initial diagnoses were follicular lymphoma in

17 patients (44%) and small lymphocytic lymphoma in nine patients (23%; Table 1). Patients had received a median number of four prior regimens (range, one to nine) and 11 patients (28%) had undergone previous stem-cell transplantation. All patients had received prior rituximab.

Treatment

Patients received SAR3419 as an intravenous undiluted infusion at a rate of 1 mL/min for 30 minutes, increased to 3 mL/min in the

Fig 2. Pharmacokinetics of SAR3419. (A) Mean SAR3419 plasma concentration-time profiles after single intravenous infusion in semilogarithmic scales. (B) Mean SAR3419 and metabolite plasma concentration-time profiles after single intravenous infusion in semilogarithmic scale at 160 mg/m². SD, standard deviation.

absence of infusion reactions. The median duration of infusion at the recommended dose was 125 minutes (range, 68 to 189 minutes). Systematic prophylaxis with a histamine blocker (ie, diphenhydramine) and an antipyretic/analgesic was used. A total of 154 cycles were administered in 39 patients, ranging from 10 mg/m² to 270 mg/m². One patient treated at 160 mg/m² died before completing the first cycle, on day 11 of cycle 1. The remaining 38 patients completed at least one cycle of treatment. Sixteen patients (41%) completed all six scheduled cycles of treatment (Table 2). Treatment was discontinued before completing the planned six cycles owing to adverse events (n = 6), progression of disease (n = 16), treatment with stem-cell transplantation (n = 1), or investigator/patient choice (n = 4).

Of 39 patients treated in the study, 23 patients were enrolled onto the dose-escalation phase at the following doses: 10 mg/m² (n = 1), 20 mg/m² (n = 3), 40 mg/m² (n = 3), 80 mg/m² (n = 3), 160 mg/m² (n = 4), 208 mg/m² (n = 7), and 270 mg/m² (n = 2) every 3 weeks. Of 39 patients in the safety population, 37 were evaluable for DLT, except two patients, both of whom were treated at the dose of 160 mg/m². One of those two patients died on day 11 of cycle 1. The second patient completed cycle 1, experienced thrombocytopenia that worsened at day 32, and received cyclophosphamide and rituximab on the same day. Because the new drugs could induce severe thrombocytopenia, the duration of the grade 4 toxicity event could not be evaluated, and the patient was considered as not evaluable for DLT and was taken off study. The DLT was reversible severe blurred vision, associated with microcystic epithelial corneal changes (Appendix Fig A1B, online-only). The MTD was 160 mg/m². An additional 16 patients were dosed at the MTD to confirm safety and collect preliminary data on efficacy at this dose. Of 15 evaluable patients who completed the first cycle of therapy, four patients (26%) had a DLT, including ocular toxicity in three patients and peripheral neuropathy in one patient, yielding a total of four (22%) of 18 patients at this dose (Appendix Table A1, online only).

Pharmacokinetics

After the first dose of SAR3419 was administered, the maximum plasma concentration of SAR3419 was generally observed at the end of infusion. Overall, SAR3419 exposure was approximately linear from 20 to 160 mg/m² and remained stable up to 270 mg/m² (Fig 2A). The terminal elimination half-life was approximately 7 days. DM4 and S-Methyl-DM4 were quantifiable starting at doses of 40 mg/m² and 80 mg/m², respectively (Appendix Table A2, online only). DM4 appeared rapidly in the plasma at concentrations about 100-fold less than those measured for SAR3419 after administration of SAR3419 (time to maximum serum concentration of 0.25 days at dose 160 mg/m²), which is likely the consequence of a slow rate of linker cleavage in plasma via thiol-disulfide exchange.¹⁵ Plasma levels of S-Methyl-DM4, the product of cellular metabolism of SAR3419,¹² were characterized by sustained concentrations and by a later time to maximum serum concentration (1.08 days at 160 mg/m²). DM4 and S-Methyl-DM4 exposures increased with dose. For the same dose, S-Methyl-DM4 exposure was higher than DM4 exposure (Fig 2B). A higher interpatient variability was observed for S-Methyl-DM4 compared with SAR3419. Anti-SAR3419 antibodies were detected in one patient on day 21 of cycle 5, with no relevant clinical symptoms. No anti-DM4 antibodies were detected in any patient.

Safety

Thirty-seven patients (95%) experienced at least one adverse event (AE), including 22 patients (56%) with a grade 3 to 4 AE. They are listed in Table 3. The only grade 3 or 4 AEs considered related to the study drug were ocular toxicity in six patients (15%), neutropenia in three patients (8%), thrombocytopenia in one patient (3%), and peripheral sensory neuropathy in two patients (6%). Six patients experienced at least one serious AE, including acute graft-versus-host disease, ascites, atrial flutter, disease progression, dyspnea, fatigue, hypotension, memory impairment, ocular toxicity, pneumonia, postherpetic neuralgia, renal failure, tremor, and ureteric obstruction.

Table 3. Common AEs According to Dose Level (n = 39)

AE	No. of Patients by Dose Level With AEs of Any Grade							Total No. of Patients (any grade)		Grade 3 or 4 AEs	
	10 mg/m ² (n = 1)	20 mg/m ² (n = 3)	40 mg/m ² (n = 3)	80 mg/m ² (n = 3)	160 mg/m ² (n = 20)	208 mg/m ² (n = 7)	270 mg/m ² (n = 2)	No. of Patients	%	No. of Patients	%
Fatigue	0	0	2	1	12	3	0	18	57	0	
Eye disorders	0	0	1	1	9	5	2	17	44	6	15
Peripheral neuropathy	0	0	1	0	10	6	0	17	44	3	8
Diarrhea	0	0	1	1	7	5	1	15	38	0	
Nausea	0	0	1	0	7	3	0	11	28	0	
Decreased appetite	0	1	1	0	5	0	0	7	18	0	
Dyspnea	0	0	1	0	5	1	0	7	18	1	3
Headache	0	0	1	0	4	1	0	6	15	0	
Pyrexia	0	1	1	0	3	1	0	6	15	0	
Contusion	1	1	0	0	3	1	0	6	15	0	
Neutropenia	0	0	0	1	2	2	0	5	13	4	10
Constipation	0	0	1	1	3	1	0	5	13	0	
Arthralgia	0	1	1	0	2	1	0	5	13	0	

NOTE. Listed are AEs reported in at least 10% of patients. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Abbreviation: AE, adverse event.

Only the grade 4 ocular toxicity was considered related to the study drug. In this patient, vision reversed to baseline within 3 days and the corneal epithelial changes resolved completely.

Ocular toxicity was the main severe toxicity related to study drug, and relationship to study drug was established in 17 of 18 patients experiencing an AE of ocular toxicity. Of these 17 patients, seven patients experienced grade 2, five experienced grade 3, and one experienced grade 4 toxicities. The primary ocular symptom was blurred vision ($n = 16$). The most common finding was bilateral corneal epitheliopathy with microcystic appearance, typically starting at the periphery of the cornea in a ring-like fashion, migrating toward the pupillary axis with occasional whitish clumping at the epithelial level (Appendix Figure A1, online only). Corneal toxicities typically occurred after the second or subsequent doses and were reversible in all patients. Patients experienced blurred vision primarily owing to irregular astigmatism induced by the corneal epitheliopathy. The toxicity in many of these patients required a dose delay of 1 to 2 weeks to allow for recovery of visual symptoms to baseline (Appendix Table A3, online only). When additional doses were administered after one event, corneal toxicity was recurrent with subsequent cycles but again was reversible in all patients.

Efficacy

Tumor response was assessed at each center by CT in all patients and additionally by PET scan for a majority of patients. Of 35 patients evaluable for efficacy, 26 patients (74%) demonstrated a reduction from baseline in their tumor sizes, ranging from 5.7% to 100%. Except for the lowest dose cohort (10 mg/m²), at least one patient in each dose cohort showed a reduction in tumor size (Fig 3A). Twenty-six patients (74%) demonstrated reduction in their tumor measurements (Fig 3B), of whom six patients achieved partial or complete remissions. Seven (47%) of 15 patients with rituximab-refractory disease demonstrated reduction in their tumor measurements (Fig 3C).

The six responders had been treated with SAR3419 at 80 mg/m² or higher. The overall response rate was 23.5% for the 17 evaluable patients at the MTD, and the overall response rate was 30% for patients with follicular lymphoma. As assessed by CT, there were two complete remissions (CRs), one unconfirmed complete remission, and three partial remissions. All six responding patients had a PET scan at baseline and during treatment. Integrated CT and PET scan results were available for five patients, three of whom had CRs. For the sixth patient, the PET scan showed a CR at the sixth cycle, but the results of the CT scan were not available. All responding patients received six cycles of treatment. An initial response was observed at cycle 2 in three patients, cycle 4 in one patient, and cycle 6 in two patients. In one patient, partial remission observed at cycle 2 was converted to CR during additional cycles. The time to response ranged from 4.6 to 17.4 weeks, and the duration of response ranged from 13.9 to at least 33.1 weeks. Two patients were still on follow-up for response duration as of the clinical cutoff date. Time to progression in responding patients ranged from 27.9 to at least 44.0 weeks.

DISCUSSION

In this first-in-human phase I clinical study, we demonstrated that the novel ADC targeting CD19, SAR3419, has promising clinical activity in patients with relapsed CD19+ B-cell lymphoma. Our study adds to

Fig 3. Clinical activity of SAR3419 in 35 evaluable patients with relapsed CD19+ B-cell lymphoma (A) by dose level, (B) by histologic subtype, and (C) by rituximab sensitivity. DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma.

the growing body of evidence demonstrating clinical utility of ADC for the treatment of a variety of cancers, including lymphoma.^{1,16,17}

In our study, the MTD of SAR3419 was found to be 160 mg/m² (approximately 4.3 mg/kg) every 3 weeks. This dose is well within the range of MTDs (approximately 2 to 6 mg/kg) that have been reported for other ADCs bearing a tubulin-agent payload. For

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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