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A Dose-Escalation Study of SAR3419, an Anti-CD19 Antibody Maytansinoid Conjugate, Administered by Intravenous Infusion Once Weekly in Patients with Relapsed/Refractory B-cell Non-Hodgkin Lymphoma

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Abstract

Purpose: To determine recommended dose, dose-limiting toxicity, safety profile, pharmacokinetics, preliminary antitumor activity, and exploratory pharmacodynamics of SAR3419, an antibody–drug conjugate targeting CD19, administered alone by intravenous infusion weekly (qw), in a dose-escalation phase I study in patients with refractory/relapsed (R/R) non-Hodgkin lymphoma (NHL).

Experimental Design: Patients with R/R CD19$^+$ B-NHL were treated with escalating doses of SAR3419 repeated qw for eight to 12 doses. On the basis of clinical evidence of late or cumulative toxicities, the study protocol was amended to test an "optimized" administration schedule consisting of four qw doses followed by four biweekly (q2w) doses (qw/q2w) at the recommended dose with the intent of reducing drug accumulation.

Results: Forty-four patients were treated on seven dose levels ranging from 5 to 70 mg/m^2. SAR3419 recommended dose was determined as 55 mg/m^2 qw. Twenty-five patients received the qw/q2w schedule at 55 mg/m^2, which showed an improved safety profile compared with the qw schedule. Antilymphoma activity was observed with both schedules in around 30% of patients with either indolent or aggressive diseases. SAR3419 displayed a long terminal half-life (approximately 7 days) and a low clearance (approximately 0.6 L/d), with no dose effect. The qw/q2w schedule allowed limiting accumulation with a decrease in SAR3419 plasma trough and average concentrations by around 1.4-fold compared with the qw schedule.

Conclusion: While administered weekly, SAR3419 is well tolerated and active. The qw/q2w schedule that shows an improved safety profile and preserves antilymphoma activity is selected for clinical phase II studies. *Clin Cancer Res; 20(1); 213–20. ©2013 AACR.*

Introduction

CD19 is the earliest differentiation antigen of the B lineage and is ubiquitously expressed on all types of B lymphocytes except plasma cells, thereby representing an attractive target for B-cell non-Hodgkin lymphomas (NHL) or leukemia of B-cell origin (10–15). SAR3419 is an antibody–drug conjugate (ADC) that targets selectively B-cells through a high-affinity binding to CD19. The ADC is created by conjugation of the humanized monoclonal immunoglobulin G (IgG1) antibody huB4 to the maytansinoid DM4, a potent inhibitor of tubulin polymerization and microtubule assembly, at the vinca-alkaloid site (such as in common intravenous chemotherapeutic agents vincristine, vindesine; refs. 16–18). Attachment of potent maytansinoids to an antibody via an optimized hindered disulfide bond provides a stable linkage in the bloodstream while keeping the potential to release active drug inside target cells (9,19). Thus, ADCs can be considered tumor-activated prodrugs (TAP; refs. 20–21). The targeted delivery approach of SAR3419 is based on the premise that conjugation of a monoclonal antibody specific to a tumor antigen with an anticancer drug will render the drug inactive in the bloodstream. SAR3419 is therefore acting mainly through direct cytotoxicity (microtubule disruption) when DM4 is

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Translational Relevance

Antibody–drug conjugates (ADC) are a new class of active monoclonal antibodies (mAb) in development for the treatment of hematologic cancers and solid tumors (1). Most of those developed for B-cell malignancies target CD19 or CD22 (2–8). SAR3419 is a humanized monoclonal immunoglobulin G (IgG1) antibody targeting CD19 attached with DM4, a tubulin inhibitor, which has been tested in B-cell lymphoma and acute lymphoblastic leukemia (9). SAR3419 phase I showed that the dose of 55 mg/m^2 is associated with efficacy when infused every week for 8 weeks, but also associated with late toxicities. An "optimized" administration schedule consisting of four weekly infusions followed by four biweekly infusions (qw/q2w) showed the same activity without this late toxicity. SAR3419 is a new interesting ADC deserving further development in B-cell malignancies.

released into cells (22–23). Several TAPs are currently undergoing clinical evaluation, mainly targeting antigens of lymphoid cells (24–30).

In preclinical studies, SAR3419 showed potent and targeted activity against CD19$^+$ tumor cells in various *in vitro* and *in vivo* models producing dose–response activity and complete tumor regressions (31, 32). Clinical evidence of activity has been initially observed in patients with refractory/relapsed (R/R) CD19$^+$ B-NHL in the First In Man (FIM) phase I study assessing SAR3419 administered every 3 weeks (q3w; 33). The recommended dose was 160 mg/m^2 q3w with an overall response rate of 22.2%. Clinical adverse events were manageable, including reversible corneal toxicity [dose-limiting toxicity (DLT)], peripheral sensory neuropathy, diarrhea, and nausea. Grade 3/4 hematologic abnormalities were mild. This second phase I dose-escalation study was conducted to evaluate a once weekly (qw) schedule of SAR3419 under the assumption that more frequent administrations at lower doses would improve antitumor activity and tolerance.

Patients and Methods

This study was conducted at six French sites, in accordance with Good Clinical Practice guidelines and the ethical principles based in the Declaration of Helsinki. From October 22, 2008, to February 14, 2011, a total of 69 patients were included and treated in the study.

Study population

Adult patients with R/R CD19$^+$ B-cell NHL were enrolled in this study. Other main criteria for eligibility were: ECOG performance score $\leq$2; absolute neutrophil count $\geq$1,000/μL, platelets $\geq$100,000/μL; adequate renal and liver function; at least one bidimensionally measurable disease; no chemotherapy or radiotherapy within 4 weeks and no radioimmunotherapy within 12 weeks before inclusion. There was no limit on prior regimen; patients with prior autologous and allogeneic stem cell transplantation were eligible. Patients with central nervous system lymphoma, known HIV infection, or active viral hepatitis were excluded. Each patient provided signed informed consent before enrollment.

Study design

This was an open-label phase I dose-escalation study designed to evaluate SAR3419 given weekly as a single agent by intravenous infusion, at a rate of 1 mL/min for 30 minutes increased to 3 mL/min in the absence of infusion reactions, for eight to 12 doses. Systematic prophylaxis with a histamine blocker and an antipyretic/analgesic was used. The planned starting dose-level was 10 mg/m^2/wk corresponding to a total dose of 30 mg/m^2 of SAR3419 administered over a 3-week period in the FIM study, and was identified as safe. At least 3 patients were to be included at each dose level. SAR3419 dose was escalated in successive cohorts and dose escalation was to be stopped when the maximum administered dose (MAD) was reached. MAD was defined as the lowest dose at which 2 of a maximum of 6 patients experienced drug-related DLTs during the initial 3-week period of treatment. At the maximum tolerated dose (MTD, highest dose at which no more than 1 of 6 patients experienced drug-related DLT), the cohort of interest was to be expanded to include 20 additional patients to better characterize the safety and preliminary activity of SAR3419.

DLTs were defined as any related grade 3 or 4 nonhematologic toxicity (except nausea and/or vomiting responsive to antiemetic therapy, and infusion-related hypersensitivity reactions), grade 4 neutropenia or grade 4 thrombocytopenia lasting more than 5 days, or re-treatment delay of more than 1 week due to delayed recovery from toxicity related to SAR3419. Late or cumulative toxicities observed during the treatment period were also considered for defining the recommended dose, upon agreement between the investigators and the sponsor.

A qw/q2w schedule consisting of intravenous infusion of SAR3419 at the recommended dose administered weekly for 4 weeks followed by four additional doses every 2 weeks was evaluated. The rationale for this schedule was based on the clinical evidence of grade 3 peripheral neurotoxicities with late onset (weeks 7 and 8) during the weekly schedule, supported by preliminary pharmacokinetics data showing accumulation of the ADC with a steady-state reached after four weekly administrations. It was hypothesized that this regimen had the potential to limit drug accumulation and therefore to minimize the incidence and severity of cumulative toxicities (34). The qw/q2w schedule was introduced after the recommended dose was reached with the weekly schedule and the enrollment in the expansion cohort was completed.

Therefore 2 cohorts of patients were treated with two separate schedules of administration: weekly, then a qw/q2w regimen.

Study assessments

Physical examination, electrocardiogram, complete blood cell count, serum chemistry tests, blood viral serologies, and CD19 testing were performed locally, either by flow cytometry analysis or immunochemistry, before initiation of therapy. Safety monitoring consisted of the ongoing assessment of adverse events using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. laboratory testing, vital signs, and physical examination were collected before each administration.

Tumor assessments by radiographic evaluation [Computed Tomography (CT) and positron emission tomography (PET) scan] were performed at baseline, after the last dose of SAR3419, and 6 weeks after the last dose. In the optimized schedule, an interim CT scan was added after four weekly doses. Bone marrow biopsy was done at baseline and repeated only if initially involved. Tumor-response assessment was characterized by the investigator using the International Working Group criteria (35). The revised response criteria for malignant lymphoma (36) may have been used for diffuse large B-cell lymphoma (DLBCL) to incorporate PET scan assessment to better identify complete remissions.

After treatment discontinuation, all responders were followed until disease progression or initiation of another antilymphoma treatment quarterly for a maximum of 1 year.

Pharmacokinetics

Peripheral blood samples were collected after the first dose of SAR3419 (on days 1, 2, 3, and 5), predose and end of infusion of each subsequent dose, and after the last dose (on days 1, 2, 5, 8, 15, 22±3).

Plasma concentrations of SAR3419 were determined by a validated ELISA with a lower limit of quantitation (LLOQ) of 0.250 μg/mL. This assay measured all HuB4-DM4 molecules charged with at least one DM4 molecule per antibody molecule. Plasma concentrations of DM4 and Me-DM4 were determined by a validated liquid chromatography/tandem mass spectrometry (LC/MS-MS) method with a LLOQ of 1.00 ng/mL. The following pharmacokinetic parameters were estimated by noncompartmental analysis (WinNonlin): peak concentration (C_{max}), area under the concentration curve (AUC), terminal half-life ($t_z1/2$), volume of distribution (V_{ss}), plasma clearance (CL), and average plasma concentration (C_{avg}).

Immunogenicity

Blood samples for immunogenicity assessment were collected at baseline (before first administration) and at the end of treatment. The potential immunogenicity of SAR3419 was evaluated by qualitative determination and identification of false-positive reactions for anti-SAR3419 and anti-DM4 antibodies in plasma by validated ELISA methods.

Pharmacodynamics

Obtaining an additional biopsy 24 to 48 hours after the second administration of SAR3419 was optional and proposed in a few patients who had biopsies at study entry to assess the binding/internalization process of the drug using immunohistochemistry techniques. SAR3419 was detected using anti-maytansine DM4 antibody. CD19 and two activity biomarkers, cleaved caspase-3 and phosphohistone-H3 (pHH3), were assessed on the paired biopsies to evaluate mitosis blockade and tumor cells' apoptosis, respectively.

On a second pool of available biopsies at study entry, an exploratory assessment of CD19 expression, Ki-67, pHH3, and p53 was performed to examine correlations of proliferation, mitosis, or p53 status with antitumor activity.

Table 1. Baseline demographics and disease characteristic

	Weekly schedule	Optimized schedule
	N	*N*
Age, median (range)	67 (36–82)	70 (37–85)
Male/female	30/14	12/13
ECOG PS (0/1/2)	18/21/5	13/9/3
Histology at study entry[a]		
FL	19 (43%)	7 (28%)
DLBCL	16 (36%)	9 (38%)
MCL, MZL, other	3, 4, 2	2, 2, 5
Ann Arbor stage III/IV at study entry	39 (89%)	24 (96%)
Median number of prior chemotherapy regimens (range)	3 (1–8)	2 (1–8)
Patients with prior rituximab-based therapy	43 (98%)	24 (96%)
Patients refractory to last regimen	16 (36%)	7 (28%)
Prior stem cell transplant autologous	18 (41%)	9 (38%)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma.

[a]Six missing histologies in the weekly schedule.

Statistical analysis

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

Results

Patients' characteristics

A total of 69 patients (44 weekly, 25 optimized) with R/R B-cell NHL were treated. Patients and disease characteristics are described in Table 1.

Treatment and DLTs

The median duration of the infusion at the recommended dose was 80 minutes (min, 55; max, 195). At the end of the study, it was discovered that one investigational site did not flush the intravenous line at each study drug infusion. A total of 12 patients (8 in the weekly and 4 in the qw/q2w schedules) were underdosed by 18 mg and were retrospectively reassigned to their actual dose delivered (DL). Study results are based on the actual DLs.

Forty-four patients were exposed weekly to SAR3419 at the following DLs: 5 ($n = 1$), 10 ($n = 3$), 14 ($n = 3$), 20 ($n = 4$), 28 ($n = 3$), 40 ($n = 5$), 55 ($n = 21$), and 70 ($n = 4$) mg/m^2/wk. No DLT was observed at the first seven dose levels. Out of the 6 patients that were originally thought to be treated at the highest dose level of 70 mg/m^2/wk, 1 patient experienced a DLT of grade 3 neutropenia requiring a 2-week dose delay after the second dose. No other patient at this dose had a DLT during the DLT-defined period.

However, beyond the DLT period, 2 patients each experienced one late grade 2 toxicity: reversible blurred vision with corneal deposit and left bundle branch block (LBBB) with onset after the seventh and the fifth weekly administration, respectively. These two additional events were considered clinically significant, even if not meeting the protocol DLT definition, and were considered for defining 70 mg/m^2 as the MAD.

Retrospectively, after underdosed patients were reassigned to their actual DL, it was concluded that a total of 4 patients instead of 6 were treated at the highest dose of 70 mg/m^2, including the patient who experienced the DLT of neutropenia and the second one with grade 2 LBBB. The grade 2 corneal toxicity occurred in a patient treated at 55mg/m^2. No DLT or other clinically significant event was reported during the first 3 weeks of treatment of the first 6 patients at the next lower dose level, 55 mg/m^2/wk, which was therefore determined as the recommended dose for a weekly schedule administration.

During the expansion cohort, one patient reported a serious grade 3 optic neuropathy (with symptoms of blurred vision, diplopia, and eye irritation) whose diagnosis was based on clinical evidence after 7 weekly doses of SAR3419. The event did not prevent the patient to receive the eighth dose of study drug and complete their treatment without any delay.

In another patient, grade 3 paresthesias (hands and feet) were observed after 8 doses of SAR3419 and led to permanent discontinuation. Both neurotoxicities were reversible within 6 weeks.

These two late grade 3 events at recommended dose were considered cumulative and led to implement the qw/q2w schedule. Twenty-five patients were treated with the qw/q2w schedule (4 at 40 mg/m^2, 21 at 55 mg/m^2). No DLT was reported with this regimen.

Overall, a total of 538 doses were administered in both schedules. The median number of doses for patients treated at the recommended dose was 8 with a median relative dose intensity of approximately 1.0 with either schedule.

Pharmacokinetics

Pharmacokinetic evaluation was performed on 69 patients. SAR3419 was eliminated slowly with a long plasma terminal half-life of approximately 7 days, a low clearance (about 0.6 L/d), and a low V_{ss} (about 4–9 L). After the first and the last administration, exposure to SAR3419 did not deviate from dose proportionality. In the weekly

Table 2. Related nonhematologic TEAE >10%

	Weekly schedule		Optimized schedule	
	MTD ($N = 21$)	All ($N = 44$)	MTD ($N = 21$)	All ($N = 25$)
Nervous system disorders	6 (28.5%)	8 (18.2%)	0	0
Paresthesia	5 (23.8%)	5 (11.3%)	0[a]	0
Eye disorders	7 (33.3%)	10 (22.7%)	3 (14.3%)	4 (16%)
Blurred vision	5 (23.8%)	5 (11.3%)	0[a]	0
Gastrointestinal disorders	5 (23.8%)	12 (27.3%)	7 (33.3%)	7 (28%)
Diarrhea	3 (14.3%)	8 (18.2%)	0[a]	0
Nausea	3 (14.3%)	7 (15.9%)	3 (14.3%)	3 (12.0%)
Musculoskeletal and connective tissue disorders	0	0	3 (14.3%)	3 (12%)
General disorders and administration site condition	5 (23.8%)	10 (22.7%)	6 (28.6%)	6 (24%)
Asthenia/fatigue	5 (23.8%)	10 (22.7%)	5 (23.8%)	5 (20.0%)

[a]One unique case each.

schedule, SAR3419 accumulation was observed with a less than 2-fold increase in C_{max} and AUC. Steady state was reached by week 7 at the recommended dose. The qw/q2w schedule allowed decreasing SAR3419 trough and average plasma concentrations by around 1.4-fold compared with the weekly schedule (Supplementary Table S1 and Supplementary Figs. S1 and S2).

Both DM4 and Me-DM4 were observed as circulating entities following SAR3419 administration. DM4 plasma concentrations were below the LLOQ in all patients at dose levels lower than 40 mg/m^2, whereas Me-DM4 could be quantified from 20 mg/m^2. Me-DM4 pharmacokinetic profile was characterized by sustained concentrations, whereas DM4 plasma concentrations decreased more rapidly. Both mean DM4 and Me-DM4 exposure increased with rising dose, with higher exposure for Me-DM4 than for DM4. On a molar basis, at the 55 mg/m^2 DL, DM4 and Me-DM4 accounted for about 0.2% and 3% of SAR3419 exposure, respectively.

Immunogenicity

All evaluable patients were negative for anti-SAR3419 and anti-DM4 antibodies, except 1 patient out of 41 who showed a positive response in the anti-SAR3419 and anti-DM4 assays at the end of treatment. No particular safety event could be associated with this result.

Safety

Overall, using the weekly schedule, the most frequent related treatment emergent adverse events (TEAE; Table 2) were gastrointestinal disorders in 12 (27%) patients, eye disorders in 10 (23%) patients mainly consisting of blurred vision, and asthenia/fatigue in 10 (23%) patients. Reversible paresthesias were reported in 5 (11%) patients after 7 weeks of treatment or later. Grade 3/4 related TEAEs were reported in 14 (32%) patients. Among these, the nonhematologic related TEAEs were reversible cholestasis and paresthesias (each in 2 patients), and isolated cases of gamma-glutamyltransferase increase, lobar pneumonia, allergic alveolitis (reported after the eighth dose of study treatment in a patient negative for immunogenicity assays), and optic neuropathy.

A case of progressive multifocal leukoencephalopathy was reported during the post treatment visits in a patient who received SAR3419 at the dose of 14 mg/m^2 weekly for 8 doses as fourth-line therapy. Prior treatment for lymphoma included a 17-month exposure to rituximab. The event became fatal within 4 months.

Overall, a total of 5 patients died within the weekly schedule, four deaths being related to disease progression.

Using the qw/q2w schedule at 55mg/m^2, the most frequent related TEAEs were asthenia in 5 (24%) patients and gastrointestinal disorders in 7 (33%) patients. Reversible grade 1 blurred vision and grade 1 paresthesias were reported in 1 patient each. Only two grade 3 events were reported: asthenia after the eighth dose at the recommended dose, and bilateral uveitis with associated decreased visual acuity after the second dose leading to permanent discontinuation at 40 mg/m^2. A 90% return of visual acuity was reported within 6 weeks. This patient died of an unrelated pneumopathy a month later without reporting full recovery of eye event. A total of 4 patients died within the qw/q2w schedule, 2 from disease progression and 2 from unrelated TEAE (pneumopathy and sudden death).

No allergic reaction and no alopecia were reported with either schedule. Myelosuppression consisting of non complicated neutropenia, anemia, and thrombocytopenia was minimal, whatever the considered schedule. There was no liver or renal grade 3/4 events at any DL in either schedule (Table 3).

Table 3. Hematologic, renal, and liver toxicity at recommended dose (55 mg/m^2)

	Weekly schedule ($N = 21$)			Optimized schedule ($N = 21$)		
Laboratory raw data	**All grade**	**Grade 3**	**Grade 4**	**All grade**	**Grade 3**	**Grade 4**
Leukopenia	10	0	3 (2)[a]	16	2 (1)[b]	1
Neutropenia	7	3	0	11	3 (2)[b]	3 (2)[b]
Anemia	15	4 (3)[a]	1	21	1	0
Thrombocytopenia	11	2 (1)[a]	1	12	3 (2)[b]	1 (0)[b]
ALT	12	0	0	9	0	0
AST	15	0	0	15	0	0
Alkaline phosphatase	9	0	0	10	0	0
Total bilirubin	4	1	0	4	0	0
Creatinine	6	0	0	7	0	0

Abbreviation: AST, aspartate aminotransferase.

[a]One patient reported grade 3 anemia/thrombocytopenia and grade 4 leukopenia under further anticancer treatment.

[b]Two patients received further anticancer therapy without being censored for hematologic reporting (overreporting). One patient was deviant at study entry and included with grade 3 neutropenia/leukopenia. Hematologic events occurring before administration of further antilymphoma therapies are presented in ().

Table 4. Antilymphoma activity

	Weekly schedule	Optimized schedule
ORR (CR/CRu/PR)	12/40 (30%)[a] including 2 CR and 4 Cru	7/25 (28%) including 1 CR and 3 CRu
ORR in DLBCL subtype	5/15 (33%)	3/9 (33%)
ORR in FL subtype	6/15 (40%)	2/7 (29%)
Median response duration (weeks)[b]	10 (5–77+)	37 (8–65+)

Abbreviations: CR, complete response; Cru: unconfirmed complete remission; PR, partial response.
[a]ORR at active dose (>10 mg/m^2).
[b]One responder in the weekly schedule and 5 responders in the optimized were still responding at the 1 year-follow-up cutoff date.

Antitumor activity

Using the weekly schedule, 43 patients were evaluable for efficacy (1 patient was not evaluable due to the use of different methods for tumor evaluation). Tumor shrinkage could be observed in 24 (55%) patients. Twelve patients with both indolent and aggressive NHL subtypes and treated at the doses 14 mg/m^2 or higher achieved an objective response. The objective response rate (ORR) as per Cheson 2007 criteria at the recommended dose was 33% (7 out of 21 patients). Whereas tumor shrinkage was obtained in 16 (64%) of the 25 patients treated with the qw/q2w schedule, 7 of them did achieve a response providing an ORR of around 30% in indolent and aggressive lymphomas. The median time to response with the qw/q2w schedule was 8 weeks with 5 out of 7 responders improving their initial response (after 4 weeks of treatment) with additional doses. Interestingly, while focusing on patients with rituximab-refractory disease at study entry, 9 (50%) of 18 patients in the weekly schedule, and 5 (56%) of 9 patients in the qw/q2w schedule, did get tumor reduction under treatment (Table 4).

Pharmacodynamics

The six available paired biopsies allowed showing DM4 accumulation in tumors (Figure 1), decrease in CD19 protein expression, and mitosis blockade in posttreatment biopsy revealed by increase in number of pHH3-positive tumor cells (Figure 1), confirming the mechanism of action of the drug.

While exploring the potential relationship between biomarkers and responses to treatment in 13 patients with heterogeneous lymphoma subtypes, no clear correlation between CD19 protein expression level, Ki67, P-Histone H3, p53 status, and patient response to treatment was evidenced (Supplementary Table S2). However, a trend to a correlation was observed between the level of CD19 expression and the response in 6 patients with DLBCL, which needs to be confirmed on a larger number of patients.

Discussion

The primary objectives of this phase I study were to determine the MTD/recommended dose and evaluate treatment safety. The recommended dose was established as 55 mg/m^2 administered every week for 4 weeks, followed by 4 biweekly administrations. Most adverse events were mild or moderate in intensity, reversible, and manageable. Gastrointestinal events were the most frequent toxicity between both schedules with no grade 3 or 4 observed. At the recommended dose, peripheral neuropathies (in the form of reversible paresthesias of the extremities) were observed in 6 patients (2 of grade 3) with the weekly schedule and in 1 patient (no grade 3) with the qw/q2w one. DM4, the cytotoxic component of SAR3419, is a potent antimicrotuble agent and these events are expected class effects with this kind of agents (37–43). In addition, the study patients received multiple prior chemotherapy regimens, including vinca-alkaloids and conditioning regimens associated with prior transplantation, potentially predisposing to the

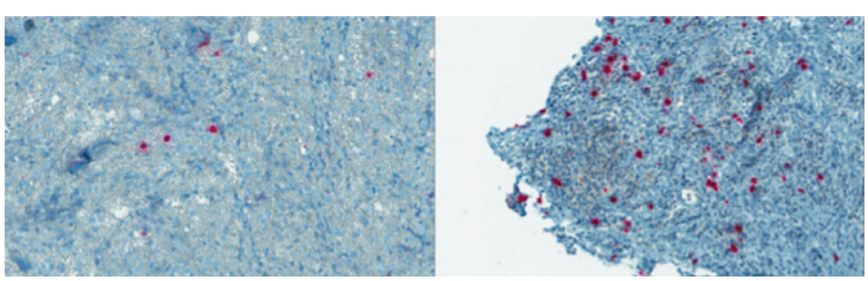

Figure 1. Pharmacodynamic assessment: DM4 detection (in brown) observed on posttreatment biopsy revealed ADC presence into the tumor. Mitosis blockade induced by DM4 was evidenced by increase in number of pHH3-positive tumor cells (in red) compared with pretreatment biopsy. The two images are of the same magnification.

development of peripheral neuropathy. Aside from the neurotoxicity, eye disorders are also commonly described with potent tubulin poisons (43–46). The reversible corneal toxicity associated with blurred vision, which appeared to be a potential safety issue in the SAR3419 FIM study is now controlled and limited to one grade 1 event of blurry vision with the qw/q2w schedule. The most common finding observed at slit lamp examination was bilateral corneal epitheliopathy with microcystic appearance typically starting at the periphery of the cornea in a ring-like fashion, migrating toward the papillary axis with occasional whitish clumping at the epithelial level. Patient's tear function and corneal thickness were largely not affected and the rest of the exam was also unremarkable.

Moreover, the minor hematotoxicity and the absence of liver events validate the proof-of-concept of the ADC providing a high therapeutic index to SAR3419.

Objective responses were observed across almost all DLs. The populations in the two phase I trials are similar, but the antitumor activity observed in this study was better compared with the previous q3w study. These results may support the hypothesis that more frequent administrations could improve SAR3419 antitumor activity. In addition, an improvement of the safety profile was also observed and the tolerability was maximized with the qw/q2w schedule.

In conclusion, the qw/q2w administration schedule of SAR3419 resulted in an encouraging ORR and a manageable safety profile. Current phase II trials are exploring the use of this schedule in a more homogenous aggressive population to confirm the clinical benefit of the drug. In addition, these data warrant the exploration of SAR3419 as single agent or in combination with other therapies in the treatment of CD19-positive hematologic malignancies.

Disclosure of Potential Conflicts of Interest

V. Ribrag, F. Laine, and B. Coiffier are consultant/advisory board members of Sanofi. Laurence Hatteville, Samira Ziti-Ljajic, Anne Caron, Sandrine Payrard, are Sanofi employees. No potential conflicts of interest were disclosed by the other authors.

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