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Phase I study of LY2469298, an Fc-engineered humanized anti-CD20 antibody, in patients with relapsed or refractory follicular lymphoma

Kensei Tobinai,[1,6] Michinori Ogura,[2] Yukio Kobayashi,[1] Toshiki Uchida,[2] Takashi Watanabe,[1] Takashi Oyama,[2] Dai Maruyama,[1] Tatsuya Suzuki,[2] Masakazu Mori,[1,7] Masanobu Kasai,[2] Damien Cronier,[3] James E. Wooldridge[4] and Minori Koshiji[5]

[1]Hematology and Stem Cell Transplantation Division, National Cancer Center Hospital, Tokyo; [2]Department of Hematology and Oncology, Nagoya Daini Red Cross Hospital, Nagoya, Japan; [3]Eli Lilly and Company, Windlesham, UK; [4]Eli Lilly and Company, Indianapolis, IN, USA; [5]Eli Lilly Japan KK, Kobe, Japan

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Patients with follicular lymphoma (FL), where position 158 of FcγRIIIa is heterozygous valine/phenylalanine or homozygous phenylalanine (F-carriers), have natural killer cells with lower binding affinity to IgG than valine homozygote patients. In addition, F-carriers show less efficacy with rituximab treatment than patients homozygous for valine. LY2469298 is a humanized IgG1 monoclonal antibody targeting CD20, with human germline framework regions, and specific amino acid substitutions engineered into the Fc region to increase effector function in antibody-dependent cell-mediated cytotoxicity. This dose-escalation, phase I study was conducted to assess the safety, pharmacokinetics and preliminary efficacy of LY2469298 in Japanese patients with previously treated, CD20-positive FL who had not relapsed or progressed within 120 days of prior rituximab. LY2469298 was administered by intravenous infusion at 100 or 375 mg/m^2 weekly for 4 weeks. Ten patients were enrolled (median age, 60 years); all had previously been treated with rituximab. Nine patients were F-carriers while one was homozygous for valine at position 158 of FcγRIIIa. No patients developed dose-limiting toxicities, and the most frequent adverse events were lymphopenia, pyrexia, leukopenia, chills and neutropenia. Five (50%) of the ten patients responded to LY2469298 treatment (three complete responses, one unconfirmed complete response and one partial response). Serum LY2469298 was eliminated in a biphasic manner and the pharmacokinetic profiles were not different from those in a preceding study in the United States. In conclusion, LY2469298 was well tolerated and clinical activity was observed in FL patients pretreated with rituximab, mostly consisting of F-carriers. Further investigation of FL is warranted. (*Cancer Sci* 2011; 102: 432–438)

Follicular lymphoma (FL) is a low-grade B-cell non-Hodgkin lymphoma for which multiple treatment options exist; however, no uniform treatment approach has been established.[1] Lymphoma cells from almost all patients with FL express CD20 antigen on their cell surface.[2] Rituximab, a chimeric monoclonal antibody that targets CD20, has emerged over the past decade as a treatment of choice for patients with FL, either as a single agent or in combination with chemotherapies.[3–10] Recently, outcomes for patients with FL have improved, and some of this improvement has been attributed to rituximab.[11–13] Despite high response rates and a long duration of disease control for most patients, the majority of patients ultimately relapse with disease that is refractory to treatment, including rituximab.[10,14]

Rituximab is hypothesized to work through multiple mechanisms, including antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and direct induction of cellular signaling pathways that result in apoptosis. ADCC, considered to be particularly important for the clinical efficacy of rituximab in B-cell non-Hodgkin lymphoma,[15] is mediated by immune effector cells, including natural killer cells, and through IgG Fc-receptors (FcγR). Substitution of phenylalanine (F) for valine (V) at one or both alleles encoding for amino acid position 158 of the FcγRIIIa (CD16a) protein has been significantly correlated with a negative outcome for FL patients treated with rituximab. For example, an FcγRIIIa protein with F at position 158 has a lower binding affinity to IgG.[16,17] In addition, patients with heterozygous (VF) or homozygous (FF) *FcγRIIIA-158* alleles (F-carriers) have a significantly lower response rate and shorter time to progression following rituximab monotherapy compared with patients with homozygous (VV) *FcγRIIIA-158* alleles.[18–20]

LY2469298 is a humanized, IgG1, anti-CD20 monoclonal antibody with human germline framework regions, a higher affinity for CD20 compared with rituximab and a limited number of amino acid substitutions in the Fc region (selected to enhance ADCC). It had approximately sixfold more potent ADCC *in vitro* with approximately 50% less CDC, compared with rituximab (data at Eli Lilly on file). Thus, LY2469298 was hypothesized to have greater activity in patients with FL compared with rituximab, particularly in *FcγRIIIA-158* F-carrier patients. Furthermore, the humanization of LY2469298 was hypothesized to decrease immunogenicity.

In the United States, a phase I study of LY2469298 was conducted in patients with FL who expressed the low affinity forms of FcγRIIIa.[21] In this US study, five dose levels (ranging from 2 to 375 mg/m^2) were investigated for safety and tolerability and the maximum tolerated dose was not reached. Therefore, the dose level of 375 mg/m^2 was selected as the recommended dose for further study.

In the present study, Japanese patients with previously treated FL were treated with four weekly doses of LY2469298 at 100 or 375 mg/m^2. The primary objectives were to investigate the safety and tolerability of repeated administrations of LY2469298 at these two dose levels for establishing a recommended dose for a phase II study. The secondary objectives were to estimate the pharmacokinetic (PK) profile of LY2469298 and to explore the clinical activity of LY2469298 in this population.

Patients and Methods

Patients. Patients were eligible if they were 20 years of age or older with histologically confirmed, CD20-positive FL,

[6]To whom correspondence should be addressed. E-mail: ktobinai@ncc.go.jp
[7]Present address: Kochi Medical School Hospital, Kochi, Japan.

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Table 1. Baseline characteristics of patients who received LY2469298

Characteristic	100 mg/m^2 (n = 3)	375 mg/m^2 (n = 7)	All (n = 10)
Median age at study entry (range) (years)	72 (50–75)	60 (39–67)	60 (39–75)
Sex, *n*; male/female	2/1	3/4	5/5
Clinical stage at study entry, *n*; I/II/III/IV	1/2/0/0	0/2/1/4	1/4/1/4
FLIPI risk group, *n*; low/intermediate/high	2/1/0	2/1/4	4/2/4
Bone marrow involvement, *n*; negative/positive	3/0	3/4	6/4
Bulky disease, *n*; 0 to <6 cm/≥6 cm	3/0	5/2	8/2
Number of prior regimens, *n*; 0/1–2/≥3	0/3/0	0/4/3	0/7/3
Prior rituximab (R), *n*; none/R alone/R-chemo	0/0/3	0/2/5	0/2/8
Refractory to rituximab†, *n*; yes/no	1/2	2/5	3/7
FcγRIIIa genotype, *n*; FF/FV/VV	1/2/0	2/4/1	3/6/1

†Latest outcome of rituximab-containing regimen was partial response, stable disease or progressive disease. For complete response, patients relapsed ≤6 months after the last rituximab infusion.
F, phenylalanine; FL, follicular lymphoma; FLIPI, follicular lymphoma international prognostic index; *n*, number of patients; V, valine.

previously treated with chemotherapy and/or rituximab (but not progressing within 120 days following the last infusion of rituximab). Patients must have provided written informed consent for the study and for genetic testing for the polymorphism of the *FcγRIIIA* gene before enrolment. *FcγRIIIA* genotyping was performed by Cogenics Inc. (Morrisville, NC, USA) using polymerase chain reaction followed by allele-specific restriction enzyme digestion. DNA isolated from peripheral blood was used for the genotyping. Eligible patients were required to have the following: at least one measurable lesion ≥1.5 cm in the longest diameter (confirmed by computed tomography [CT] scanning); Eastern Cooperative Oncology Group performance status of 0 or 1; absolute neutrophil count (ANC) >1500/mm^3; platelet count >75 000/mm^3; hemoglobin ≥8 g/dL; serum creatinine ≤1.5 × upper limit of normal (ULN); total bilirubin ≤1.5 × ULN; alkaline phosphatase ≤1.5 × ULN; and alanine transaminase ≤1.5 × ULN.

Patients were not eligible if they had the following: evidence of hepatitis B or C virus infection; clinically significant transformation to diffuse large B-cell lymphoma; known allergy to antibody therapy or any of the study drug components; active concurrent malignancy; significant cardiac complications (e.g. New York Heart Association Congestive Heart Failure class III or higher); positive test for serum cardiac troponin; active infection; a history of blood transfusion or erythropoietin treatment within 10 days prior to enrolment; a history of growth factor administration within 28 days prior to enrolment; or were positive for human immunodeficiency virus (HIV-1) infection. Patients were required to discontinue all anti-lymphoma treatments at least 30 days prior to study enrolment

Study design and treatment. This open-label, multicenter, non-randomized, dose-escalation, phase I study was designed to investigate the safety and tolerability of weekly doses of LY2469298 in patients with relapsed or refractory CD20-positive FL. The study was conducted between October 2008 and December 2009 at two institutions (National Cancer Center Hospital, Tokyo and Nagoya Daini Red Cross Hospital, Nagoya, Japan). This study was approved by the institutional review boards of the two institutions and conducted in accordance with the ethical principles of the Declaration of Helsinki.

LY2469298 was administered intravenously, at a dose of either 100 or 375 mg/m^2, four times at weekly intervals. LY2469298, supplied in a glass vial containing 1 mL at a concentration of 20 mg/mL, was diluted in normal saline to a final concentration of 1 mg/mL and given through a 0.22-μm in-line filter. The first infusion of LY2469298 was administered slowly at a rate of ≤25 mg/h and increased by up to 50 mg/h every 30 min. Subsequent infusions could be administered at an initial rate of up to 100 mg/h with increments every 30 min until the 300 mg/h rate was reached. All patients were premedicated with antipyretic analgesic (e.g. acetaminophen) and anti-histamine (e.g. diphenhydramine) given 30 min before the infusion.

Table 2. Most common† and all grade 3 or 4 drug-related adverse events

Adverse events‡	100 mg/m^2				375 mg/m^2				Total
	Any grade	Grade 1–2	Grade 3	Grade 4	Any grade	Grade 1–2	Grade 3	Grade 4	
Hematological									
Lymphopenia	3	1	2	0	7	2	3	2	10
Leukopenia	1	1	0	0	6	6	0	0	7
Neutropenia	1	1	0	0	4	2	1	1	5
Thrombocytopenia	0	0	0	0	2	2	0	0	2
Non-hematological									
Pyrexia	1	1	0	0	7	7	0	0	8
Chills	2	2	0	0	5	5	0	0	7
Headache	1	1	0	0	2	2	0	0	3
Oropharyngeal discomfort	0	0	0	0	3	3	0	0	3
Epigastric discomfort	0	0	0	0	2	2	0	0	2
Fatigue	0	0	0	0	2	2	0	0	2
Respiratory tract infection	1	1	0	0	1	1	0	0	2
Increased LDH	0	0	0	0	2	2	0	0	2
Increased CRP	0	0	0	0	2	2	0	0	2
Rash	0	0	0	0	2	2	0	0	2

†Treatment-related adverse events reported in ≥20% of patients are listed. ‡All events that were possibly related to LY2469298 were reported.
CRP, C-reactive protein; LDH, lactic dehydrogenase.

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Table 3. Number of patients developing infusion-related toxicities

Infusion	100 mg/m^2				375 mg/m^2			
	1st	2nd	3rd	4th	1st	2nd	3rd	4th
No. patients infused	3	3	3	3	7	6	6	6
Grade 1†	1	0	0	0	4	1	0	1
Grade 2†	2	0	0	0	3	0	0	0
Grade 3†	0	0	0	0	0	0	0	0
Grade 4†	0	0	0	0	0	0	0	0
Total	3	0	0	0	7	1	0	1

†Common Terminology Criteria for Adverse Events Version 3.0.

Table 4. Best overall response by *FcγRIIIA-158* genotype

FcγRIIIA-158 Genotype	100 mg/m^2			375 mg/m^2		
	FF	*VF*	*VV*	*FF*	*VF*	*VV*
No. patients	1	2	0	2	4	1
CR	0	1	0	0	1	1
CRu	0	0	0	0	1	0
PR	0	0	0	1	0	0
SD	1	1	0	1	1	0
PD	0	0	0	0	1	0

CR, complete response; CRu, complete response unconfirmed; PR, partial response; SD, stable disease; PD, progressive disease.

Infusion-related reactions were monitored continuously between the start of the infusion and 60 min after the infusion was completed. Infusions were to be slowed or suspended for any clinically significant infusion-related reaction.

The treatment plan was to enroll at least three patients at the 100 mg/m^2 dose level, and up to six patients at this level if one patient experienced a dose-limiting toxicity (DLT), before escalating to the higher dose level. If no more than one of six patients experienced a DLT at 100 mg/m^2, the dose was to be escalated to 375 mg/m^2, which was established as the recommended phase II dose in a phase I study conducted in the United States.[21] The protocol treatment was to be discontinued for a patient if any of the following occurred: disease progression; appearance of DLT; unacceptable toxicity; withdrawal of informed consent; serious deviation of study compliance; loss to follow up; or investigator's discretion.

Study evaluation. Safety and toxicity were evaluated by monitoring laboratory assessments and the incidence, severity and type of adverse events (AE). All AE were graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0. Patients were monitored for DLT from the initial infusion to 2 weeks after the last infusion (5 weeks). The DLT was defined as any grade 3 or greater drug-related AE, with the following modifications: grade 3 hematological toxicity was defined as an ANC nadir of ≥500 to <1000/mm^3, or a decrease in platelet count or hemoglobin of 50–74% from the lower limit of normal or the baseline value, whichever was less; cardiac toxicity of grade 3 or greater that occurred during the DLT evaluation period. The following were defined *a priori* as not DLT: grade 3 infusion reactions (e.g. fever, rigors, bronchospasm, urticaria and hypotension) that were transient and resolved without sequelae; grade 3 tumor lysis syndrome that was transient and resolved without sequelae. An enzyme-linked immunosorbent assay (ELISA) was used to detect the level of human anti-human antibody (HACA) to LY2469298 in serum sampled before the first infusion and 5 weeks after the last infusion (performed by Millipore Corporation, St Charles, MO, USA).

Response assessment. Response assessments after treatment with LY2469298 were performed 9 and 21 weeks after the last infusion. The efficacy of LY2469298 was evaluated according to the International Workshop Response Criteria for Non-Hodgkin Lymphomas.[22] Objective responses included complete response (CR), unconfirmed CR (CRu) and partial response (PR). Baseline evaluation included disease-related symptoms (B symptoms), radiographic examination using CT and bone marrow biopsy.

B-lymphocyte monitoring and pharmacokinetic (PK) analysis. B-lymphocytes were monitored using FACS analysis (performed by Mitsubishi Chemical Medience Corporation, Tokyo, Japan) using an anti-CD19 monoclonal antibody conjugated to a fluorescent probe. Samples for both the PK and CD19 analyses were obtained before each infusion; 1 and 3–5 days after the first infusion; 1 and 3–5 days, 2, 5, 9 and 21 weeks after the last infusion; and at withdrawal from the study. Serum levels of LY2469298 were determined using an enzyme-linked immunosorbent assay (performed by the Charles River Laboratories Preclinical Services Montreal Inc, Senneville, QC, Canada).

Pharmacokinetic parameter estimates for LY2469298 were calculated by standard noncompartmental methods of analysis using WinNonLin Professional Version 5.0.1 (Pharsight, Cary, NC, USA). Noncompartmental parameters, such as the maximum concentration (C_{max}), the elimination half-life ($t_{1/2}$), area under the concentration–time curve (AUC), apparent clearance (CL), apparent volume of distribution (V_z), and mean residence time (MRT) of LY2469298 were reported following the fourth dose administration. The C_{max} was taken from the observed data. The apparent terminal rate constant (λ_z) was calculated from the regression of log concentration versus time over the terminal log-linear portion of the concentration–time profile. $T_{1/2}$ was calculated as $\ln 2/\lambda_z$. The AUC were calculated using the log-linear trapezoidal rule. Following the fourth dose, $AUC_{0\text{-tlast}}$ was calculated from 0 h post-dose to the last sampling point, and $AUC_{0\text{-}\tau}$ was calculated from 0 to 168 h post-dose. The CL was calculated as $Dose/AUC_{0\text{-}\tau}$, V_z was calculated as $Dose/(\lambda_z \times AUC_{0\text{-}\tau})$ and MRT was calculated as $(AUMC_{0\text{-}\tau} + \tau[AUC_{0\text{-}\infty} - AUC_{0\text{-}\tau}])/AUC_{0\text{-}\tau}$ − infusion duration/2, where AUMC is the area under the moment curve.

Results

Patients. Ten Japanese patients with CD20-positive FL were enrolled in the present study (Table 1). Most patients had both clinical stage II or IV FL at study entry, and most of the advanced-stage patients (clinical stage III or IV) were enrolled in the 375 mg/m^2 cohort. The median age of the ten enrolled patients was 60 years. All patients had received one or more prior treatments of rituximab alone or rituximab-containing chemotherapy, and three of these were judged to be refractory to rituximab. The median number of prior regimens was two (range, 1–9). The Follicular Lymphoma International Prognostic Index (FLIPI)[23] identified four patients at low risk, two at intermediate risk and four at high risk. Among the ten enrolled patients, only one patient had *FcγRIIIA-158VV* alleles; the remaining nine patients were F-carriers (six with *FcγRIIIA-158VF* alleles and three with *FcγRIIIA-158FF* alleles). Six of the F-carriers (four with *FcγRIIIA-158VF* alleles and two with *FcγRIIIA-158FF* alleles) and one *FcγRIIIA-158VV* patient were enrolled in the 375 mg/m^2 cohort. All three patients in the 100 mg/m^2 cohort were F-carriers (two with *FcγRIIIA-158VF* alleles and one with *FcγRIIIA-158FF* alleles).

Safety. Nine patients completed all four infusions and were evaluable for DLT. One patient was suspended from study treatment after the first infusion and did not continue because the study was suspended to resolve an issue with preparation of the study drug. The patient had no significant safety problems

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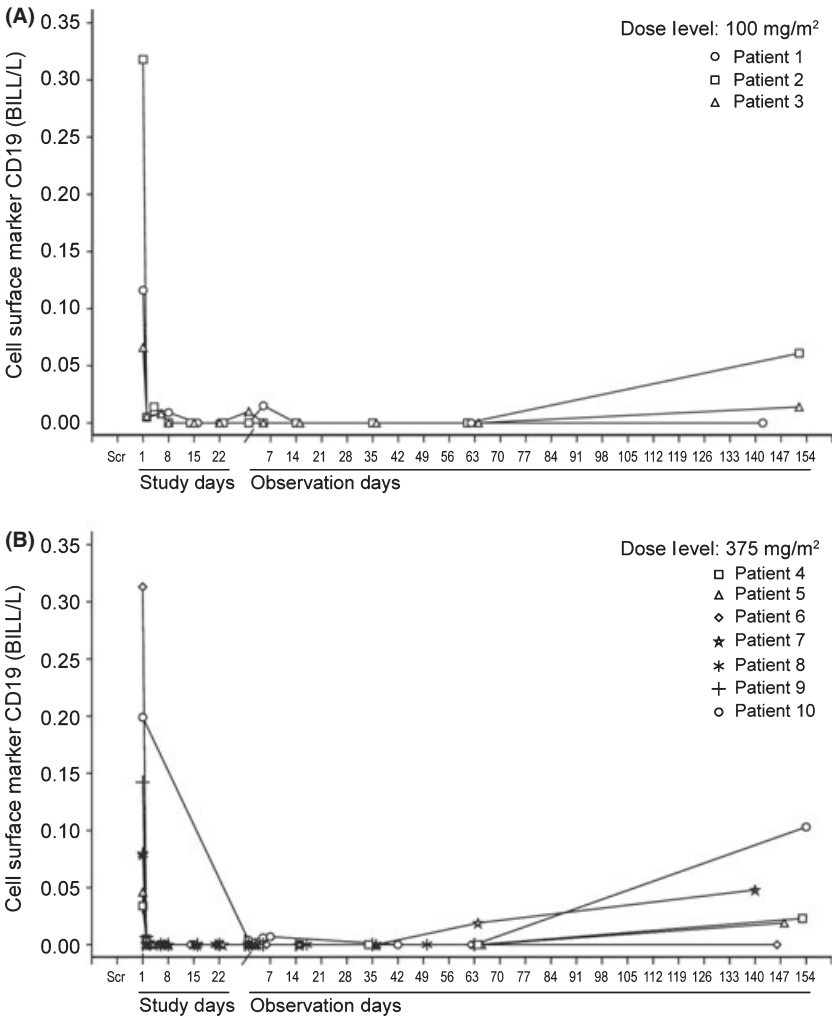

Fig. 1. Time course of the cell counts of CD19-positive B-lymphocytes in each patient. (A) The 100 mg/m^2 LY2469298 cohort. (B) The 375 mg/m^2 LY2469298 cohort. Study days = the number of days on the study starting with the first infusion. Observation days = the number of days after the last infusion. Scr, Screening.

Table 5. Pharmacokinetic parameters of LY2469298 after the last infusion

	Parameter								*FcγRIIIA-158* Genotype	Best overall response
	$t_{1/2}$ (h)	$AUC_{0-\tau}$ (μg·h/mL)	$AUC_{0\text{-tlast}}$ (μg·h/mL)	$AUC_{0-\infty}$ (μg·h/mL)	C_{max} (μg/mL)	MRT (h)	CL (L/h)	V_z (L)		
100 mg/m^2										
Patient 1	613	20300	106000	131000	157.55	987	0.00732	6.47	FF	SD
Patient 2	313	16400	50600	52600	105.45	452	0.0100	4.52	VF	CR
Patient 3	199	12400	37200	37400	121.53	413	0.0108	3.09	VF	SD
Mean†	337	16100	58400	63600	126	569	0.00924	4.49		
CV (%)†	62	25	58	72	21	51	21	38		
375 mg/m^2										
Patient 4	195	35100	88200	88700	389.47	329	0.0216	6.08	VF	SD
Patient 5	133	52400	138000	138000	400.56	352	0.00989	1.90	VF	CRu
Patient 6	451	57000	224000	249000	552.11	641	0.0101	6.55	VV	CR
Patient 7	28.8	9760	9950	9950	190.23	45.2	0.0665	2.76	FF	SD
Patient 8	130	52100	111000	111000	446.37	268	0.0112	2.10	VF	PD
Patient 9	499	49700	171000	192000	351.65	560	0.0125	9.02	VF	CR
Mean†‡	238	48600	139000	146000	423	407	0.0125	4.28		
CV (%)†‡	73	19	37	43	17	38	33	81		

†Geometric mean and CV%. ‡Excluding data from patients 7 (outlier) and 10 (early discontinuation of treatment). $AUC_{0-\tau}$, area under the concentration versus time curve during one dose interval; $AUC_{0\text{-tlast}}$, area under the concentration versus time curve from time zero to time *t*, where *t* is the last time point with a measurable concentration; $AUC_{0-\infty}$, area under the concentration versus time curve extrapolated to infinity; CL, total body clearance; C_{max}, maximum serum concentration; CV, coefficient of variation; MRT, mean residence time; $t_{1/2}$, terminal elimination half-life; V, volume of distribution; CR, complete response; CRu, complete response unconfirmed; PR, partial response; SD, stable disease; PD, progressive disease.

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and was excluded from DLT evaluation. No DLT were observed between the first infusion and 2 weeks after the last infusion.

Treatment-related AE were observed in all ten patients treated with at least one dose of LY2469298. Most of the AE were grade 1 or 2, and the most common AE were hematological (lymphopenia, leukopenia, neutropenia) or infusion-related (pyrexia, chills) (Table 2). The only encountered AE of grade 3 or greater were lymphopenia and neutropenia; neither of the patients with neutropenia required treatment with granulocyte colony-stimulating factor. There were no deaths, serious AE or discontinuations due to AE.

Infusion-related toxicities were observed in all patients; all of these were grade 2 or less, with the majority limited to the first infusion (Table 3). Most infusion-related toxicities were similar to those previously reported after rituximab treatment,[24–27] except for increased heart rate and somnolence, both of which were mild and manageable. In four patients (two in each cohort) the infusion rate was adjusted due to infusion-related toxicities. HAHA was not detected in the serum samples from all patients before and up to the 5 weeks after the last infusion.

Responses. Across both cohorts, objective responses were observed in the following five of ten patients: three patients (one in the 100 mg/m^2 cohort; two in the 375 mg/m^2 cohort) achieved CR; one patient (375 mg/m^2 cohort) achieved CRu; and one patient (375 mg/m^2 cohort) achieved PR (Table 4). Responses were observed at both dose levels: four of seven patients at 375 mg/m^2 and one of three at 100 mg/m^2. The patient with homozygous *FcγRIIIA-158VV* alleles achieved CR after receiving 375 mg/m^2. Among the F-carriers, four of nine patients achieved objective responses (three of six patients in the 375 mg/m^2 cohort). Among the heterozygous F-carriers, an objective response was observed in three of six patients (two CR and one CRu). Among the homozygous F-carriers, an objective response was observed in one of three patients (PR).

There was a quick and sustained reduction in the number of CD19+ B-lymphocytes in the peripheral blood following the first infusion, which began to recover during the 21-week observation period (Fig. 1).

Pharmacokinetics (PK). All ten patients were included in the PK analysis except patient 7 (dosed at 375 mg/m^2). The rate of LY2469298 disappearance from serum in this patient was very

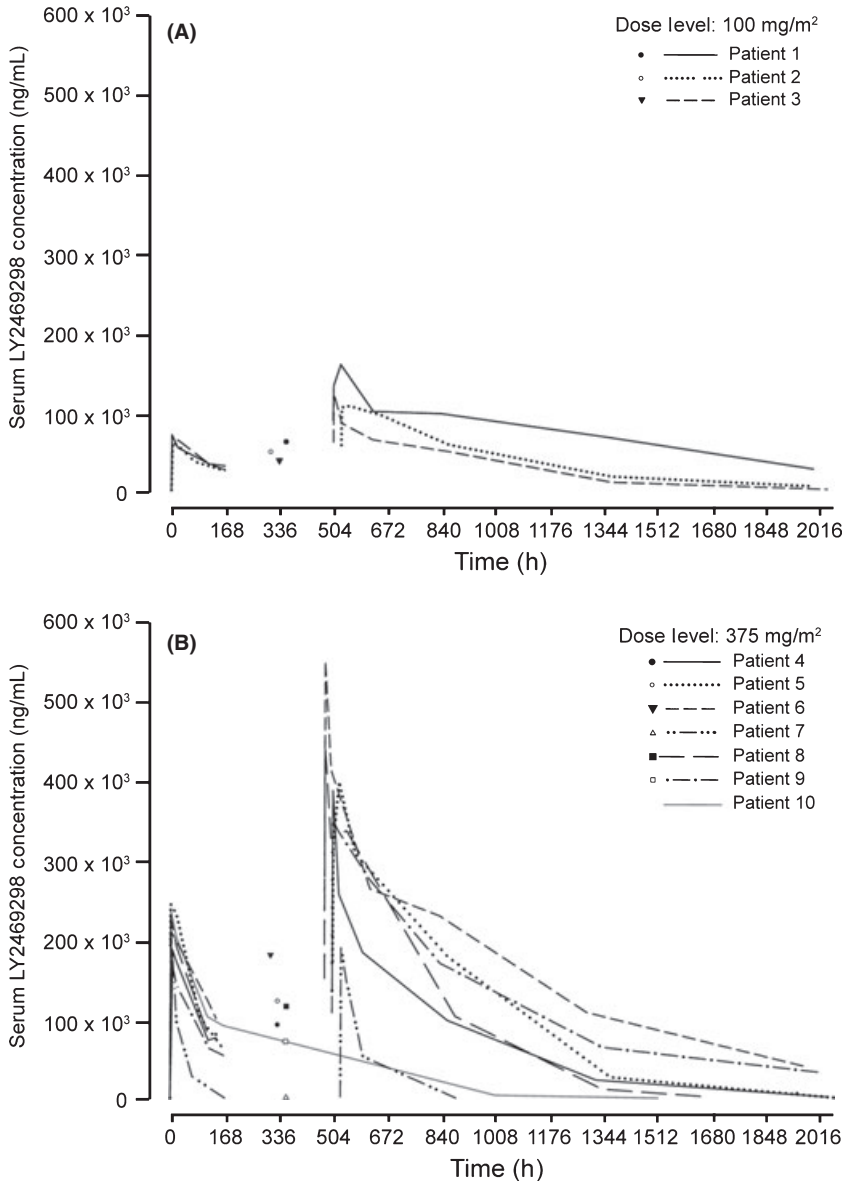

Fig. 2. Time course of serum concentrations of LY2469298 in each patient. (A) 100 mg/m^2 LY2469298 cohort. (B) 375 mg/m^2 LY2469298 cohort. Note that patient 10 discontinued from the study treatment after the first infusion, and patient 7 had a very short elimination half-life.

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fast and characterized by a very short elimination half-life. In the remaining nine patients, LY2469298 was detected in serum until 12 weeks after the last infusion. Observed individual and mean PK parameters for LY2469298 in serum after the last infusion are summarized in Table 5. Individual PK profiles are shown in Figure 2. The area under the concentration versus time curve (AUC) and maximum observed drug concentration (C_{max}) increased with the dose. The mean terminal elimination half-lives ($t_{1/2}$) of the antibody in the 100 and 375 mg/m^2 cohorts were 337 h (199–613) and 238 h (130–499), respectively. Other PK parameters were also similar between the two dose levels and were characterized by a moderate to high interpatient variability. No relationship between response and PK parameters was found.

Discussion

The primary aim of the present study was to investigate the safety and tolerability of LY2469298 administered in four weekly doses of 100 or 375 mg/m^2 to Japanese patients with CD20-positive FL who had received rituximab alone or rituximab-containing regimens. One patient with homozygous *FcγRIIIA-158VV* alleles, six with heterozygous *FcγRIIIA-158VF* alleles, and three with homozygous *FcγRIIIA-158FF* alleles were enrolled. Even though the sample number was small, the frequency of each polymorphism was within the range of previous reports.[15,17]

The safety profile of LY2469298 in Japanese patients was similar to that observed in a previous phase I study in non-Japanese patients.[21] The administration of LY2469298 was well tolerated at the higher dose of 375 mg/m^2 in all patients enrolled. No DLT were observed and the most frequent AE were hematological or infusion related, and all observed AE were manageable. Based on these results, a weekly dose of 375 mg/m^2 was recommended for further studies of LY2469298.

Among the three patients who achieved CR, two had heterozygous *FcγRIIIA-158VF* alleles and one had homozygous *FcγRIIIA-158VV* alleles. It is noteworthy that one patient with heterozygous *FcγRIIIA-158VF* alleles, who had received eight prior regimens, achieved CRu. Regarding the single patient who discontinued the study treatment after the first infusion, a PR was observed at day 148. As hypothesized, CD19-positive peripheral blood B-lymphocytes were depleted in all patients examined.

The PK parameters for LY2469298 when administered to Japanese patients were not remarkably different from those observed in a phase I study of LY2469298 in the United States[21] or those described in the literature for rituximab in Japanese patients.[26–29] For example, LY2469298 was eliminated from serum in a biphasic manner, and both the AUC and C_{max} increased with the dose. One patient with bone marrow involvement and hepatomegaly was noted to have a much shorter elimination half-life of LY2469298 despite treatment at the higher dose of 375 mg/m^2. While in a phase I study of rituximab reported by Maloney *et al.*,[24] one patient who had a large tumor burden, including splenomegaly, also had a shorter elimination half-life of rituximab, within 10 days after the infusion. However, given the limited sample size in the present study, it is difficult to determine the possible cause of the shorter elimination half-life of LY2469298 in this particular patient.

Recent studies suggest that *FcγRIIIA-158VF* polymorphism may have a predictive value for the efficacy of IgG1 antibodies in other tumor types.[30–32] Therefore, antibody engineering of the Fc-region, similar to that used in LY2469298, may be useful to enhance the efficacy of other therapeutic IgG1 antibodies. In the era of personalized medicine, further evaluation of *FcγRIIIA-158VF* polymorphism may be useful to predict and improve the efficacy of therapeutic IgG1 antibodies and ultimately improve the outcomes for patients with FL and other diseases treated with antibodies.

In conclusion, LY2469298, a humanized IgG1 monoclonal antibody with an increased affinity to CD20 and greater ability to mediate ADCC than rituximab *in vitro*, was well tolerated by Japanese patients with previously treated FL (who had received rituximab alone or rituximab-containing regimens). Objective responses were observed in 50% of the patients, mostly consisting of F-carriers. Further studies will determine the exact role of LY2469298 in the treatment of FL patients.

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Disclosure Statement

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