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ORIGINAL ARTICLE

A phase I/II study of ofatumumab (GSK1841157) in Japanese and Korean patients with relapsed or refractory B-cell chronic lymphocytic leukemia

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Abstract The tolerability, efficacy, safety and pharmacokinetic profile of a human anti-CD20 monoclonal antibody, ofatumumab, was evaluated in this phase I/II study in patients with relapsed or refractory B-cell chronic lymphocytic leukemia (B-CLL). This study consisted of two parts. Tolerability was assessed in phase I (Part A), while the overall response rate (ORR) was assessed in phase II (comprising Parts A and B). Three patients were enrolled in Part A, and another seven patients were enrolled in Part B. Ofatumumab 300 mg was given at the first infusion, followed by seven weekly and four monthly infusions of 2000 mg. No patients experienced dose-limiting toxicity, and tolerability was confirmed. The ORR was 70 %. The most commonly reported adverse events (AEs) were leukopenia, neutropenia, and lymphopenia. No patients discontinued the study due to AEs. Plasma concentrations of ofatumumab prior to the next weekly dose increased steadily over the 8 weeks and did not reach steady state; with monthly dosing, pre-dose ofatumumab concentrations decreased. Inter-patient variability of pharmacokinetic parameters was larger after the first dose than after the later dose. In conclusion, this phase I/II study suggests that ofatumumab provides favorable safety and efficacy in Japanese/Korean patients with relapsed or refractory B-CLL.

Keywords Ofatumumab · Phase I/II study · Relapsed or refractory chronic lymphocytic leukemia

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Introduction

Ofatumumab (Genmab A/S, Denmark) is an IgG1κ human monoclonal antibody (mAb) that targets a unique epitope on the CD20 molecule that encompasses both small and large extracellular loops [1, 2]. Ofatumumab induce lysis of several B-cell lines and primary B-cell chronic lymphocytic leukemia (B-CLL) cells, including rituximab-resistant cells [1, 3]. Ofatumumab induces B-cell depletion via complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) [1].

Clinical studies of ofatumumab have been conducted in Western countries [4–11]. The safety and efficacy of ofatumumab monotherapy were initially evaluated in a phase I/II study in heavily pretreated patients with relapsed or refractory B-CLL. The study showed that first infusions of 100, 300, or 500 mg plus 3 weekly infusions of 500, 1000,

or 2000 mg were well tolerated, and at the highest dose administered, the overall response rate (ORR) was 50 % [10]. These promising results were confirmed in a pivotal phase II study of ofatumumab monotherapy in patients with B-CLL refractory to fludarabine and alemtuzumab (FA-ref) and in those with bulky lymphadenopathy refractory to fludarabine but not suitable for treatment with alemtuzumab. Patients received first infusion of 300 mg, followed by 7 weekly infusions of 2000 mg and 4 monthly infusions. The results were favorable for both efficacy and safety [8, 11] and resulted in approval of ofatumumab for the treatment of FA-ref B-CLL in the United States and Europe.

Furthermore, a phase I study in patients with small lymphocytic lymphoma and CLL in Japan has confirmed the tolerability of ofatumumab as monotherapy at 500 and 1000 mg [12].

To further determine the clinical significance of ofatumumab at 2000 mg in Japanese and Korean patients with B-CLL, a phase I/II study was conducted.

Materials and methods

Patients

Eligible patients were 20 years or older with relapsed or refractory B-CLL previously treated with any anti-CLL therapy. The diagnosis of B-CLL required the presence of at least 5000/μL B lymphocytes in the peripheral blood with positive findings for CD5, CD19, CD20, and CD23 tests according to the National Cancer Institute-Sponsored Working Group (NCI-WG) response guidelines [13].

This study was performed in accordance with Good Clinical Practice. The protocol was approved by the Institutional Review Board of each participating institution, and conformed to the provisions of the Declaration of Helsinki in 2008. All patients gave a written informed consent.

Study design

This study was planned as an open-label, non-randomized, multicenter phase I/II study, consisting of 2 parts (Part A and Part B).

The primary objective in Part A was to evaluate the tolerability of ofatumumab at 2000 mg in Japanese patients. In Part A and Part B, the primary objective was to assess the ORR to 2000 mg ofatumumab in Japanese and Korean patients.

Ofatumumab at 300 mg was given at the first infusion, followed by 7 weekly infusions of 2000 mg and then 4 monthly infusions of 2000 mg for a total of 12 infusions over 24 weeks. Safety and efficacy were evaluated until 48 weeks after the first infusion.

Thirty to 120 min prior to each infusion of the study drug, all patients received oral acetaminophen 400 mg or equivalent, and oral or intravenous antihistamine (e.g. cetirizine hydrochloride 10 mg, or equivalent). Before the first and second infusions, all patients also received intravenous glucocorticoid equivalent to 100 mg of prednisolone (30–120 min prior to infusion of the study drug). After the third infusion, glucocorticoid was given if clinically indicated in the opinion of the investigator.

Tolerability evaluation

Dose-limiting toxicity (DLT) was defined as grade 3 or greater non-hematological toxicity (excluding grade 3 nausea and vomiting and grade 3 infusion reaction), or grade 3 infusion reaction persisting until the next day despite pre-medication and appropriate management, or grade 4 hematological toxicity of neutropenia lasting $\geq$7 days and febrile neutropenia (fever for more than 2 days and grade 4 neutropenia).

DLT was monitored from the start of treatment until 7 days after the 8th infusion. DLT was evaluated in the first 3 patients. When 1/3 or 2/3 patients met one of the DLT criteria, additional 3 patients were enrolled to evaluate DLT. If 0/3 or $\leq$2/6 patients met one of the DLT criteria, the dose was judged as tolerable.

Efficacy evaluation

The primary efficacy endpoint was the ORR. Assessment of response was according to NCI-WG guidelines. Secondary efficacy endpoints included progression-free survival (PFS), duration of response, time to response, improvement in constitutional symptoms, and improvement in Eastern Cooperative Oncology Group (ECOG) performance status.

The efficacy was evaluated by an independent review committee (IRC).

Safety evaluation

Adverse events (AEs) were reported throughout the study period and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The serum samples for the human anti-human antibody (HAHA) testing were collected at baseline prior to the treatment and at week 24 and week 48 post-treatment. The formation of HAHA against ofatumumab was assessed using a validated electro chemiluminescence bridging immunoassay method on a

Meso Scale Discovery 6000 plate reader (MSD, Gaithersburg, MD, USA).

The mean serum titers of IgA, IgG, and IgM antibody were assessed at baseline and at week 8, week 24, and week 48.

"Infusion reactions" were determined based on clinical judgment. All adverse events observed within 24 h after the end of infusion were reviewed by a clinical reviewer.

Pharmacokinetic parameters

Blood samples were collected from 8 patients enrolled in Part A and Part B of the study for pharmacokinetic (PK) examinations. PK parameters were derived by non-compartmental analysis, based on the time after the start of infusion. The following PK parameters were calculated for each patient, from available data from the first, 8, and 12th infusions: maximum plasma concentration (C_{max}), time to observed maximum drug concentration (t_{max}), plasma half-life at terminal phase ($t_{1/2}$), area under the concentration–time curve (AUC_{0-inf} and AUC_{0-tau}), clearance (CL), volume of distribution at steady state (V_{ss}), and mean residence time (MRT).

Statistical analysis

This study neither asserted nor tested any statistical hypotheses.

Results

Study population

A total of 10 patients with relapsed or refractory B-CLL were enrolled into this study and received ofatumumab at 3 centers in Japan and at 1 center in Korea. Three patients were enrolled in Part A and were evaluated for tolerability. After the tolerability of ofatumumab at 2000 mg was confirmed, 7 patients were enrolled in Part B. The median age of the patients was 67 years (range 55–74 years). The median number of prior anti-CLL therapy was 1 (range 1–3). Eight of 10 patients were treated with fludarabine or with fludarabine combination therapy as the prior therapy (Table 1). No patients were treated with rituximab. Seven of 10 patients completed study treatment, and 3 patients prematurely discontinued from the study (Table 2). Among 3 patients, one withdrew just before the administration of the 12th infusion. The patient refused further study treatment due to positional vertigo and tinnitus although the investigator considered withdrawal unnecessary. The remaining 2 withdrew during the follow-up period after the last infusion.

Table 1 Demographic characteristics

	$N = 10$ [n (%)]
Age in years at screening	
Median (range)	67 (55–74)
Age groups	
<65 years	2 (20)
≥65 years	8 (80)
≥75 years	0
Sex	
Female	3 (30)
Male	7 (70)
Regimen number of prior anti-CLL therapy	
Median (range)	1 (1–3)
Summary of prior anti-CLL therapy	
Fludarabine	8 (80)
Cyclophosphamide	5 (50)
Prednisolone	2 (20)
Chlorambucil	1 (10)
Vincristine	1 (10)
Rituximab	0 (0)
Time from diagnosis[a] (years)	
Median (range)	5.2 (1.4–7.8)
Binet staging at screening	
A	2 (20)
B	4 (40)
C	4 (40)
Modified Rai staging at screening	
Low risk (stage 0)	1 (10)
Intermediate (stage I, II)	5 (50)
High risk (stage III, IV)	4 (40)

CLL chronic lymphocytic leukemia

[a] Data in 8 patients

Table 2 Patients disposition

	$N = 10$ [n (%)]
Completed	7 (70)
Discontinued	3 (30)
Primary reason for discontinuation	
Investigator discretion	2 (20)[a]
Withdrew consent	1 (10)[b]

[a] Due to subsequent anti-CLL treatments

[b] Due to subject's willingness to discontinue study treatment

Tolerability

None of the patients experienced DLT. Ofatumumab at 2000 mg was well tolerated in Japanese patients.

Efficacy

Primary endpoint

The ORR was 70 % [95 % confidence intervals (CI), 35–93 %] as assessed by the IRC (Table 3). All of the 7 responders achieved partial remission (PR). Clinical improvements in components of the response are shown in Table 4.

Table 3 Overall Response Rate

Response	$N = 10$ [n (%)]
Complete remission	0
Partial remission	7 (70)
Stable disease	3 (30)
Progressive disease	0
Overall response rate	7 (70)
95 % Confidence interval (%)	(35–93)

Table 4 Improvement in each component

	$N = 10$ [n (%)]
Responders	7 (70)
Lymphadenopathy	
≥50 % reduction	2/9 (22)
Absence of lymphadenopathy (>1.5 cm in the greatest diameter)	1/9 (11)
Hepatomegaly	
≥50 % reduction in the size of the liver	3/5 (60)
No hepatomegaly	3/5 (60)
Splenomegaly	
≥50 % reduction in the size of the spleen	6/10 (60)
No splenomegaly	6/10 (60)
Blood lymphocytes	
≥50 % decrease in peripheral blood lymphocyte count from baseline	10/10 (100)
Peripheral lymphocyte <4000/μL	10/10 (100)
Marrow	
50 % reduction in marrow infiltrate, or B-lymphoid nodules	6/10 (60)
<30 % lymphocytes, no B-lymphoid nodules.	0/10 (0)
Platelet count	
>100000/μL or 50 % improvement from baseline	2/4 (50)
>100000/μL	1/4 (25)
Hemoglobin	
>11.0 g/dL or 50 % improvement from baseline	0/1 (0)
>11.0 g/dL	0/1 (0)
Neutrophils	
>1500/μL or 50 % improvement from baseline	–
>1500/μL	–
Constitutional symptoms	
Absence of constitutional symptoms	1/1 (100)

Secondary endpoints

The median duration of response and PFS could not be estimated with a median follow-up of 47.2 weeks. The median time to response was 8.1 weeks. One patient had constitutional symptoms at the baseline assessment, which resolved by week 5. The ECOG performance status remained unchanged from baseline in all patients.

Safety

AEs experienced by more than one patient are shown in Table 5.

Commonly reported AEs were leukopenia, lymphopenia, and neutropenia, each occurring in 6 of 10 patients (60 %). No deaths were reported. One patient (Korean) experienced a serious AE of enteritis with vomiting,

Table 5 Adverse events (adverse events experienced by ≥ two patients)

Adverse event	$N = 10$	
	Any grade n (%)	Grade 3/4 n (%)
Hematological		
Leukopenia	6 (60)	3 (30)
Lymphopenia	6 (60)	2 (20)
Neutropenia	6 (60)	4 (40)
Thrombocytopenia	4 (40)	0
Anemia	2 (20)	0
Non-hematological		
Increase of blood lactate dehydrogenase	5 (50)	0
Rash	5 (50)	0
Hyperglycemia	4 (40)	3 (30)
Infusion-related reaction	4 (40)	0
Nasopharyngitis	3 (30)	0
Peripheral sensory neuropathy	3 (30)	0
Increase of aspartate aminotransferase	2 (20)	0
Constipation	2 (20)	0
Diarrhea	2(20)	0
Eczema	2 (20)	0
Fatigue	2(20)	0
Herpes zoster	2 (20)	0
Influenza	2 (20)	0
Decrease of total protein	2 (20)	0
Pyrexia	2 (20)	0
Stomatitis	2 (20)	0
Positional vertigo	2 (20)	0

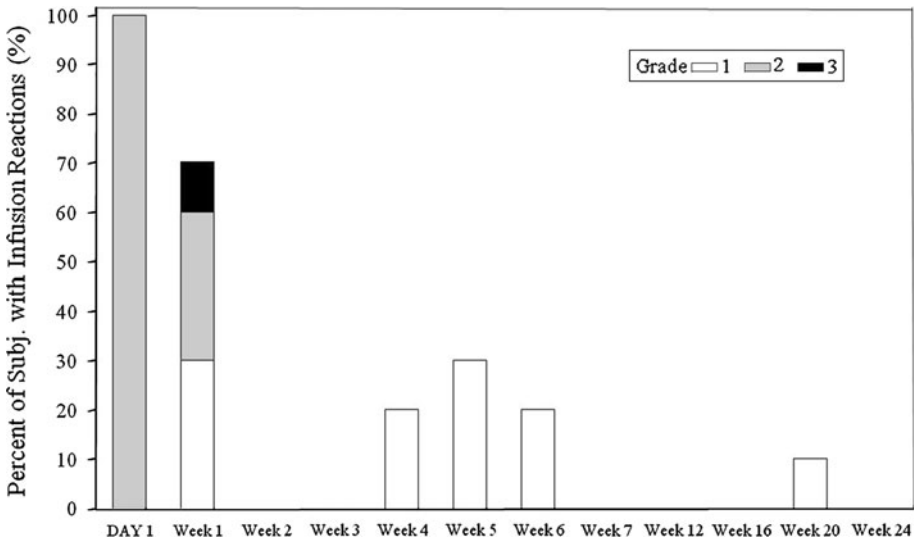

Fig. 1 Infusion reactions by grade

diarrhea, and fever (38.9 °C) during the study, but the event was considered to be unrelated to ofatumumab.

All 10 patients experienced "infusion reactions" (Fig. 1). All but one infusion reaction were of grade 1 or grade 2. One patient had grade 3 hypotension during the infusion. The most common "infusion reactions" were rash and infusion-related reaction, each reported in 4 of 10 patients (40 %), and pyrexia in 2 of 10 patients (20 %). The majority of the "infusion reactions" occurred on day 1 (first infusion) or week 1 (second infusion) and resolved within 24 h of onset. The percentage of patients experiencing "infusion reactions" decreased over the course of treatment.

Infections were reported in 7 of 10 patients; all but one infection were grade 1 or 2.

The most common infections were nasopharyngitis, reported in 3 of 10 patients (30 %), herpes zoster and influenza, each occurring in 2 of 10 patients (20 %); and gastroenteritis, oral herpes, pneumonia, and upper respiratory tract infection, each occurring in 1 of 10 patients (10 %).

The mean serum titers of IgA, IgG, and IgM antibody remained almost unchanged from the start of ofatumumab infusion until week 48.

Seven of 10 patients tested negative in the HAHA assay. The other 3 patients were not able to be evaluated.

Pharmacokinetic parameters

Mean (+SD) ofatumumab plasma concentration–time plot in all patients (7 Japanese and 1 Korean) who received ofatumumab 300 mg at the first infusion, followed by 7 weekly infusions of 2000 mg and then 4 infusions of 2000 mg every 4 weeks, is shown in Fig. 2. The summary of pharmacokinetic parameters is shown in Table 6.

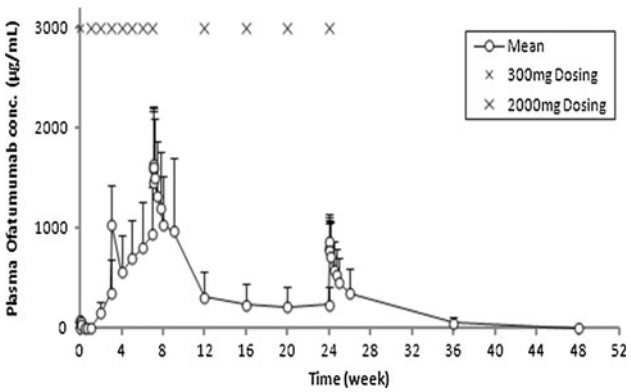

Fig. 2 Mean (+SD) plasma concentration of ofatumumab–time plots

Plasma concentration of ofatumumab prior to next weekly dose increased steadily over the 8 weeks but did not reach steady state; with monthly dosing, pre-dose ofatumumab concentrations decreased from 834 µg/mL prior to the 8th weekly infusion to 122 µg/mL prior to the fourth monthly infusion. Inter-patient variability of PK parameters was larger after the first dose when compared with later dose. Geometric mean of C_{max} of ofatumumab at the first infusion (300 mg), at the last weekly infusion (8th, 2000 mg), and at the last monthly infusion were 71, 1691 and 865 µg/mL, respectively. AUC was 1524 h µg/mL at the first infusion (300 mg, AUC_{0-inf}), 200904 h µg/mL at the last weekly infusion (8th infusion, 2000 mg, AUC_{0-168}), and 216678 h µg/mL at the last monthly infusion (12th infusion, 2000 mg, AUC_{0-672}).

In the patient in Korea, C_{max} was 76 µg/mL at the first infusion (300 mg), 1354 µg/mL at the last weekly infusion (8th infusion, 2000 mg), and 618 µg/mL at the last monthly interval infusion (12th infusion, 2000 mg). AUC was 1879 h µg/mL at the first infusion (300 mg, AUC_{0-inf}), 136612 h µg/mL at the last weekly infusion (8th infusion,

Table 6 Pharmacokinetic parameters of ofatumumab

	Day 1 300 mg ($N = 8$)	Week 7[a] 2000 mg ($N = 8$)	Week 24[b] 2000 mg ($N = 7$)
C_{max} (μg/mL)	71 (44–115)	1691 (1332–2146)	865 (659–1136)
C_{min} (μg/mL)	–	834 (539–1291)	122 (29–518)[c]
AUC[d] (h μg/mL)	1524 (599–3878)	200904 (139158–290046)	216678 (114238–410979)
$t_{1/2}$ (h)	9.6 (5.0–18.3)	332 (224–492)	300 (182–495)
CL (mL/h)	197 (77–501)	10.0 (6.9–14.4)	9.2 (4.9–17.5)
V_{ss} (mL)	3607 (2269–5735)	1333 (927–1917)	3069 (2123–4437)
MRT (h)	18.3 (10.4–32.3)	478 (333–686)	464 (264–817)

Geometric mean (95 % confidence interval)

[a] After final (8th) weekly dose

[b] After final (4th) monthly dose

[c] $N = 8$

[d] AUC_{0-inf} for day 1, AUC_{0-168} for week 7, AUC_{0-672} for week 24

2000 mg, AUC_{0-168}), and 90209 h μg/mL at the last monthly interval infusion (12th infusion, 2000 mg, AUC_{0-672}). C_{max} and AUC in the patient in Korea were within or just below the lower limit of the 95 % CI of all patients.

Discussion

This study was conducted to evaluate the tolerability, efficacy, safety, and PK profile of ofatumumab at 2000 mg in Japanese and Korean patients with relapsed or refractory B-CLL.

All 10 patients experienced "infusion reactions" such as rash and pyrexia. "Infusion reactions" were prevalent during the first 2 doses, but largely subsided with subsequent infusions (Fig. 1), as expected based on the previous Western clinical studies in patients with B-CLL [10, 11]. Most of the "infusion reactions" were of grade 1 or 2 and only one patient developed grade 3 hypotension. Dose interruption was required by 8 patients on day 1 and by 3 patients at week 1. However, all patients were able to recommence dosing and receive the complete planned ofatumumab infusion. These results suggest that the "infusion reactions" were manageable.

Infections were reported in 70 % of patients. The majority of the infections (86 %) were grade 1 or 2 in severity except for 1 patient who developed grade 3 pneumonia. Since the pneumonia occurred more than 4 months after the final administration of ofatumumab, it was judged unrelated to ofatumumab by the investigator. The incidence and severity of infections observed in this study were as expected based on experience in Western CLL patients. In the Western phase II study, infections were reported in 67 % of patients. The most infectious AEs (74 %) occurring during treatment were grade 1 or 2 in severity, and the incidence of grade 3 or 4 infections was reported at the expected level, considering prior treatment, extent of disease, and immunosuppression among these patients [11, 14].

The ORR of 70 % (95 % CI 35–93 %) in the present study is comparable with that of 47 % (95 % CI 40–54 %) in Western phase II study [8].

Clinical improvements for a minimum duration of 2 months, based on components of the NCI-WG guidelines, are shown in Table 4. The rates of complete resolution were 60 % (3 of 5 patients) for hepatomegaly and 60 % (6 of 10 patients) for splenomegaly, and the rate of substantial reduction in lymphadenopathy was 11 % (1 of 9 patients). These results were consistent with those in the Western phase II study; complete resolution of hepatomegaly in 20 of 39 patients (51 %), splenomegaly in 30 of 76 patients (39 %), and lymphadenopathy in 17 of 129 patients (13 %) [11]. The improvement rate for lymphadenopathy was lower than that for other components; however, all patients showed 8–82 % reductions in lymphadenopathy (Fig. 3), indicating activity.

Ofatumumab pharmacokinetics in this study in Japanese and Korean patients with CLL was consistent with ofatumumab pharmacokinetics in Western patients with CLL receiving the same dosing regimen [15]. At the eighth weekly infusion (2000 mg), geometric mean values of ofatumumab C_{max}, CL, and $t_{½}$ were 1482 μg/mL, 9.5 mL/h, and 15.8 days in Western patients [15] and were 1691 μg/mL, 10.0 mL/h, and 13.8 days in Japanese and Korean patients in this study.

The study population in this study was patients with CLL previously treated with any anti-CLL treatment, while that in the Western Phase II study mainly consisted of patients with CLL refractory to fludarabine and alemtuzumab, and CLL refractory to fludarabine with bulky (>5 cm) lymph nodes. Although the differences in the study population

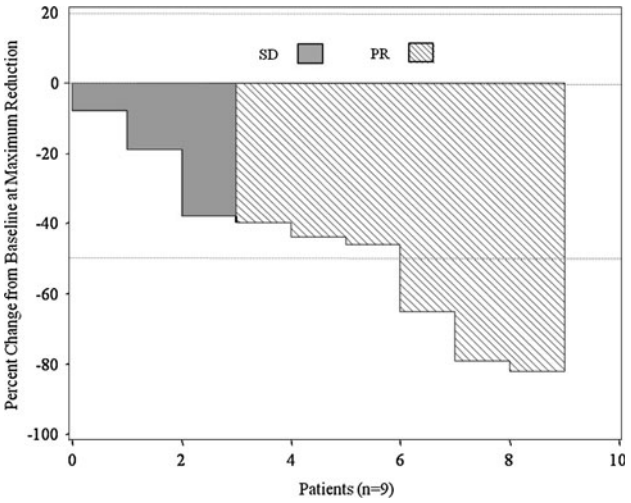

Fig. 3 Reduction of sum of products of the greatest diameters in lymphadenopathy

exist, no apparent differences in the profile of ofatumumab safety, efficacy and PK were suggested in this study.

In conclusion, Ofatumumab provided favorable safety and efficacy in Japanese and Korean patients with relapsed or refractory B-CLL. Although this was a small study, the results indicate that ofatumumab monotherapy is as clinically active and well tolerated in Asian patients as it is in non-Asian patients. This phase I/II study suggests that ofatumumab is a promising agent for the treatment of relapsed or refractory B-CLL.

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Conflict of interest Yoshiaki Ogawa, Michinori Ogura, Tatsuya Suzuki, Kiyoshi Ando, Toshiki Uchida, Yukari Shirasugi have no conflicts of interest relevant to the subject matter or materials included in this manuscript. Kensei Tobinai has received honoraria from Genzyme Japan K.K., Janssen Pharmaceutical K.K., and Glaxo-SmithKline K.K. Je Hwan Lee has no conflict relevant to the subject matter or materials included in this manuscript. Masazumi Kase and Koichi Katsura are employees of GSK. Tomomitsu Hotta has no conflict relevant to the subject matter or materials included in this manuscript.

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