

Pomalidomide alone or in combination with dexamethasone in Japanese patients with refractory or relapsed and refractory multiple myeloma

Kosei Matsue,¹ Hiromi Iwasaki,² Takaaki Chou,³ Kensei Tobinai,⁴ Kazutaka Sunami,⁵ Yoshiaki Ogawa,⁶ Mari Kurihara,⁷ Shuichi Midorikawa,⁷ Mohamed Zaki,⁸ Thomas Doerr⁸ and Shinsuke Iida⁹

¹Division of Hematology/Oncology, Department of Medicine, Kameda Medical Center, Kamogawa; ²Center for Cellular and Molecular Medicine, Kyushu University Hospital, Fukuoka; ³Department of Internal Medicine, Niigata Cancer Center Hospital, Niigata; ⁴Department of Hematology, National Cancer Center Hospital, Tokyo; ⁵Department of Hematology, National Hospital Organization, Okayama Medical Center, Okayama; ⁶Department of Hematology/Oncology, Tokai University School of Medicine, Isehara; ⁷Celgene KK, Tokyo, Japan; ⁸Celgene Corporation, Summit, New Jersey, USA; ⁹Department of Hematology and Oncology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

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Correspondence

Kosei Matsue, Division of Hematology/Oncology, Department of Medicine, Kameda Medical Center, Kamogawa, Chiba 296-8602, Japan.

Tel: +81-4-7092-2211; Fax: +81-4-7099-1253;

E-mail: koseimatsue@gmail.com

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This phase 1, open-label, dose-escalation study investigated the tolerated dose (recommended dose), safety, efficacy, and pharmacokinetics of pomalidomide alone or pomalidomide plus low-dose dexamethasone in Japanese patients with refractory or relapsed and refractory multiple myeloma. Twelve patients were enrolled. Patients received pomalidomide 2 mg (Cohort 1) or 4 mg (Cohort 2) orally on day 1 and days 3–21 of a 28-day cycle. The tolerated dose of pomalidomide was determined to be 4 mg given on days 1–21 of a 28-day cycle. Efficacy outcomes with pomalidomide plus low-dose dexamethasone were consistent with those of previous studies. Responses (partial response or better) were achieved by three patients (25%; 1 [17%] in Cohort 1 and 2 [33%] in Cohort 2), and the median time to response was 6.4 months overall (9.0 months for Cohort 1 and 4.2 months for Cohort 2). The median progression-free survival was 5.5 months overall (5.1 months for Cohort 1 and not reached for Cohort 2). The most frequently occurring grade ≥ 3 adverse events were neutropenia (67%), anemia (25%), lymphopenia (25%), and pneumonia (25%), consistent with previous studies of pomalidomide plus low-dose dexamethasone in refractory or relapsed and refractory multiple myeloma. Further investigation of pomalidomide is recommended for Japanese patients with refractory or relapsed and refractory multiple myeloma. This study was registered with ClinicalTrials.gov (NCT01568294).

Patients with relapsed and refractory multiple myeloma (RRMM) who have had treatment failure with lenalidomide and bortezomib have a poor prognosis characterized by shortened overall survival (OS).⁽¹⁾ For patients who have exhausted therapy with lenalidomide and bortezomib, there is a substantial unmet need for new therapeutic options. Pomalidomide is the newest approved immunomodulatory agent with direct anti-myeloma and stromal cell inhibitory effects.^(2,3) Preclinical experience has shown that multiple myeloma (MM) cell lines retain their sensitivity to pomalidomide plus dexamethasone but become resistant to lenalidomide plus dexamethasone when treated on a long-term basis.⁽⁴⁾ A prior phase 1, open-label, dose-escalation study assessed the maximum tolerated dose (MTD) of pomalidomide in patients with MM refractory to ≥ 2 lines of therapy or relapsing after previous therapy.^(5,6) In this study, the MTD was determined to be 2 mg for continuous dosing and 5 mg for alternate-day dosing.^(5,6) A phase 1b/2 study of pomalidomide alone or in combination with dexamethasone for the treatment of RRMM carried out in the USA and Canada (MM-002) assessed the MTD in the phase 1b portion of the trial and confirmed an MTD of 4 mg.⁽⁷⁾ Pomalidomide plus low-dose dexamethasone has shown significant

improvements in progression-free survival (PFS) and OS in clinical studies.⁽⁸⁾ Pomalidomide plus low-dose dexamethasone has also shown high response rates and durable responses in phase 1/2 clinical studies.^(7,9–11)

In the pivotal phase 3 MM-003 clinical trial comparing pomalidomide plus low-dose dexamethasone with high-dose dexamethasone in patients with RRMM, PFS was 4.0 vs 1.9 months ($P < 0.0001$) and OS was 12.7 vs 8.1 months ($P = 0.0285$), respectively (median follow-up, 10.0 months).⁽⁸⁾ Based on the results of the MM-002 and MM-003 trials, pomalidomide was approved in the USA and European Union (in combination with low-dose dexamethasone), respectively, for the treatment of patients with RRMM who received ≥ 2 prior treatments including lenalidomide and bortezomib and progressed on treatment (EU) or within 60 days following completion of their last line of treatment (USA).^(12,13)

Clinical studies have also previously assessed the pharmacokinetic (PK) parameters of pomalidomide in healthy individuals and patients with RRMM in populations not restricted to Japanese patients.^(5,14) In healthy volunteers, pomalidomide showed rapid absorption after it was taken orally (time to maximum plasma concentration [C_{max}] was approximately 2–3 h).⁽¹²⁾

Additionally, systemic exposure of pomalidomide as measured by area under the plasma concentration–time curve (AUC) was shown to be proportional to the administered dose.⁽¹²⁾ Here we report the results of MM-004, a phase 1, open-label, dose-escalation study designed to determine the tolerated dose (TD; recommended dose) of pomalidomide in Japanese patients with RRMM based on the observed MTD of pomalidomide (4 mg) in the MM-002 trial⁽⁷⁾ and assess the safety, efficacy, and PK of pomalidomide alone or in combination with low-dose dexamethasone.

Materials and Methods

Study description. This was a phase 1, multicenter, open-label, dose-escalation study to evaluate the TD (recommended dose), safety, efficacy, and PK of pomalidomide given alone or in combination with dexamethasone to Japanese patients with primary RRMM. The primary endpoint of the study was to determine the TD of pomalidomide. Secondary endpoints included efficacy, PK, and safety. Efficacy was assessed by overall response rate (ORR; \geq partial response [PR]), time to response, duration of response, and PFS. Response was assessed by the International Myeloma Working Group criteria.⁽¹⁵⁾ To ensure consistency across centers for clinical laboratory data used to assess response, a central laboratory (LSI Medicine Corporation, Tokyo, Japan) was used in this study. The Efficacy–Safety Evaluation Committee (ESEC) also evaluated efficacy as assessed by investigators. Pharmacokinetic measurements included C_{max} , estimated elimination half-life during terminal phase ($t_{1/2}$), $AUC_{0-24\text{ h}}$, apparent clearance of drug from plasma, and apparent volume of distribution during the terminal phase. Adverse events (AEs) were reported according to type, frequency, and severity. Investigators assessed the relationship of AEs to the study drug.

Patients. Patients, aged ≥ 20 years, had measurable disease (serum M-protein ≥ 0.5 g/dL or urine M-protein ≥ 200 mg/day) and were ineligible for stem cell transplant. All patients previously received ≥ 2 lines of antimyeloma therapy and had documented disease progression during or within 60 days of completing their last prior treatment. Prior therapy must have included ≥ 2 cycles of lenalidomide and ≥ 2 cycles of bortezomib, as well as adequate alkylator therapy; induction therapy followed by stem cell transplant was counted as a single therapy. Patients were required to have an Eastern Cooperative Oncology Group performance status of ≤ 2 . Patients were excluded if they had any of the following: absolute neutrophil count $< 1000/\mu\text{L}$, platelet count $< 75\,000/\mu\text{L}$ for patients in whom $< 50\%$ of bone marrow nucleated cells were plasma cells, platelet count $< 30\,000/\mu\text{L}$ for patients in whom $\geq 50\%$ of bone marrow nucleated cells were plasma cells, creatinine clearance < 45 mL/min, and grade ≥ 2 peripheral neuropathy. All patients provided informed consent before any study procedures were carried out. The study was approved by the Institutional Review Board of each study site before the study was initiated and was carried out in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice (set forth by the International Conference on Harmonisation E6 requirements).

Study design. The study consisted of four phases: (i) a screening phase; (ii) a TD identification phase; (iii) a treatment phase; and (iv) a follow-up phase. During the 28-day screening phase, patients were screened for eligibility for treatment with pomalidomide. The TD identification period was composed of two cohorts, Cohort 1 and Cohort 2, and the TD was identified

based on the number of patients experiencing dose-limiting toxicities (DLTs) during cycle 1 in each cohort. A description of DLTs is included in Table 1. Patients in Cohort 1 received a single dose of pomalidomide 0.5 mg seven days before the start of cycle 1 for PK evaluation. Beginning on the first day of cycle 1, patients in Cohort 1 received 2 mg pomalidomide orally on day 1 and days 3–21 of a 28-day cycle. The study was constructed based on a 3 + 3 design to determine the TD, based on two dose levels. Six patients per cohort were needed to evaluate PK; therefore, the total number of patients to be enrolled for this study was 12. The TD was defined as the highest dose level at which no more than two out of six patients experienced a DLT within cycle 1. A detailed depiction of the TD identification process is illustrated in Figure 1.

Following identification of the TD, both cohorts proceeded to the treatment phase, which consisted of pomalidomide 2 mg/day (Cohort 1) or 4 mg/day (Cohort 2) on days 1–21 of a 28-day cycle and dexamethasone 40 mg/day (for patients aged ≤ 75 years) or 20 mg/day (for patients aged > 75 years) on days 1, 8, 15, and 22 of a 28-day cycle. All patients concomitantly received low-dose aspirin or equivalent thromboprophylaxis for the prevention of venous thromboembolism. Treatment continued until disease progression, unacceptable toxicity, or patient withdrawal from study. During the treatment phase, pomalidomide dose reductions and dose interruptions were allowed. Upon discontinuation, patients were assessed every 3 months during the follow-up phase, which will continue until the ESEC determines that follow-up is no longer needed.

Safety assessments. The safety population (all patients who received one or more doses of study medication) was used for analysis of all safety variables. The severity of AEs was

Table 1. Dose-limiting toxicities (DLTs) used for identification of the tolerated dose of pomalidomide in Japanese patients with refractory or relapsed and refractory multiple myeloma

DLT	Description
Any grade AE	
Febrile neutropenia	ANC $< 1000/\mu\text{L}$ with a single temperature of $> 38.3^\circ\text{C}$ or a sustained temperature of $\geq 38.3^\circ\text{C}$ for > 1 h
Grade 3 AE	
Any pomalidomide-related non-hematologic AE	With exception to anorexia, fatigue, abnormal laboratory values
Transaminitis	Serum transaminase $> 5\text{--}20 \times \text{ULN}$ for ≥ 7 days
Nausea	Patients must have already received optimal treatment for symptoms
Vomiting	Patients must have already received optimal treatment for symptoms
Diarrhea	Patients must have already received optimal treatment for symptoms
Platelet count decrease	$< 50\,000\text{--}25\,000/\mu\text{L}$ with hospitalization and/or transfusion
Grade 4 AE	
Any pomalidomide-related non-hematologic AE	–
Infection	–
Neutrophil count decrease	$< 500/\mu\text{L}$ for ≥ 7 days
Platelet count decrease	$< 25\,000/\mu\text{L}$ requiring > 1 transfusion

–, no further description; AE, adverse event; ANC, absolute neutrophil count; ULN, upper limit of normal.

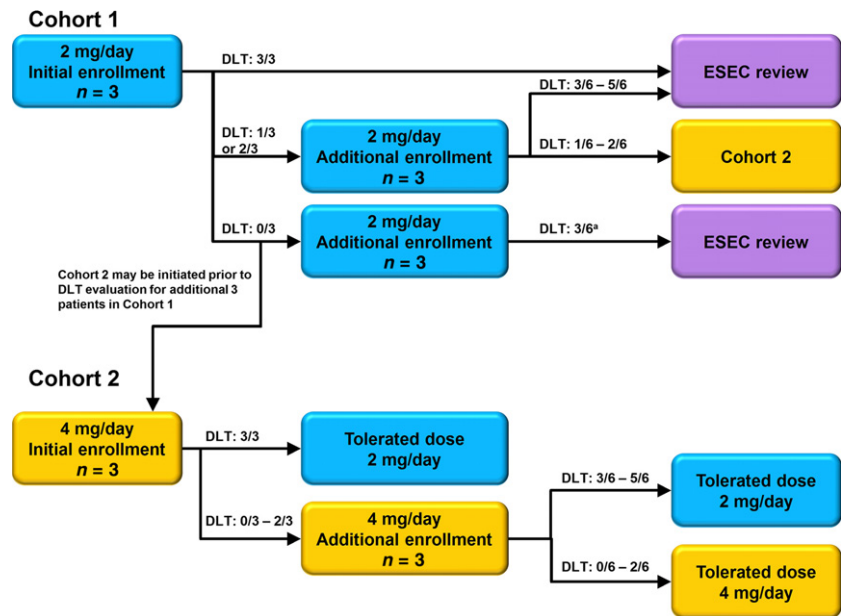


Fig. 1. Determination of the tolerated dose of pomalidomide in Japanese patients with refractory or relapsed and refractory multiple myeloma. Patients received pomalidomide 2 mg (Cohort 1) or 4 mg (Cohort 2) orally on day 1 and days 3–21 of a 28-day cycle. *In this instance, continuation of the study would be discussed at the ESEC. DLT, dose-limiting toxicity; ESEC, Efficacy–Safety Evaluation Committee.

graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Safety assessments were carried out from study entry until 28 days after study discontinuation. Safety was assessed by evaluation of AEs, monitoring and assessment for second primary malignancy, concomitant medications, venous thromboembolism monitoring, physical examination, electrocardiogram, laboratory assessments, and pregnancy counseling and testing. The ESEC also reviewed safety data throughout the trial and was responsible for advising the study sponsor regarding treatment continuation, dose modification, and termination of the study.

Statistical analysis. Patients eligible for efficacy evaluation included patients who received one or more doses of study drug and had a baseline and one or more postbaseline efficacy assessments. All patients who received one or more doses of pomalidomide and had evaluable PK data were included in the PK population. The PK parameters were calculated from pomalidomide plasma concentration–time data using non-compartmental methods. Pomalidomide plasma concentrations and PK parameters were summarized by treatment and study days using descriptive statistics. The mean (\pm SD) and individual plots of plasma concentrations vs time were determined in both linear scale and semilogarithmic scales. Dose proportionality was explored for single dose and multiple doses separately by visual inspection of data as well as by the statistical model. Software used for PK data analysis and presentation included WinNonlin Professional, version 5.2 (Pharsight Corporation, Mountain View, CA, USA) and SAS, version 9.1.3 (SAS Institute, Inc., Cary, NC, USA).

Results

Patients. The study enrolled 12 patients in total, comprising six patients in each cohort. All 12 patients were evaluable for safety and efficacy analysis. As of the data cut-off date of 19 November, 2013, five patients remained on treatment: one patient from Cohort 1 and four patients from Cohort 2 (Fig. 2). Seven patients discontinued the study due to progressive disease (five in Cohort 1 and two in Cohort 2). No patients

discontinued due to AEs and, as of the cut-off date, no patient had died during study treatment or within 30 days of discontinuation. All patients received a median of 6.5 cycles of treatment (range, 2–11 cycles). Baseline demographics are presented in Table 2. The median age was 68 years (range, 52–76 years). The majority of patients were elderly; 67% of patients were aged >65 years. Most patients (92%) did not have moderate renal impairment (RI; creatinine clearance <60 mL/min); one patient in Cohort 2 had moderate RI, and no patients in Cohort 1 had moderate RI. Patients were heavily pretreated, with a median of six prior antimyeloma therapies (range, 4–10). Three patients from each cohort received a prior thalidomide-containing treatment regimen (50% for both cohorts). All patients enrolled received prior lenalidomide and bortezomib to be eligible for inclusion. All 12 patients were refractory to lenalidomide; 10 (83%) patients were refractory to both bortezomib and lenalidomide.

Tolerated dose and efficacy assessments. The TD (recommended dose) was determined to be pomalidomide 4 mg given on days 1–21 of a 28-day cycle. One DLT of grade 4 neutropenia for ≥ 7 days was observed in one patient enrolled in Cohort 1. No DLTs were observed among patients enrolled in Cohort 2. The ORR (\geq PR) was 25% for the overall population (three patients); ORR was 17% (one patient) in Cohort 1 and 33% (two patients) in Cohort 2. In Cohort 1, one patient achieved a PR, four patients had stable disease, and one patient had progressive disease. Two patients in Cohort 2 achieved a PR, three patients had stable disease, and one patient progressed while on treatment. In the three patients who achieved a response with treatment (\geq PR by International Myeloma Working Group criteria), the median time to response was 6.4 months (9.0 months in Cohort 1 and 4.2 months in Cohort 2), with one patient in Cohort 2 achieving a response as early as 1.9 months. As of the cut-off date, no patient with a response experienced disease progression or died; therefore, the median duration of response has not been reached. The median PFS was 5.5 months for the overall population (Fig. 3). Seven patients not responding to treatment progressed or died as of the cut-off date. Among the patients enrolled in Cohort 1, five

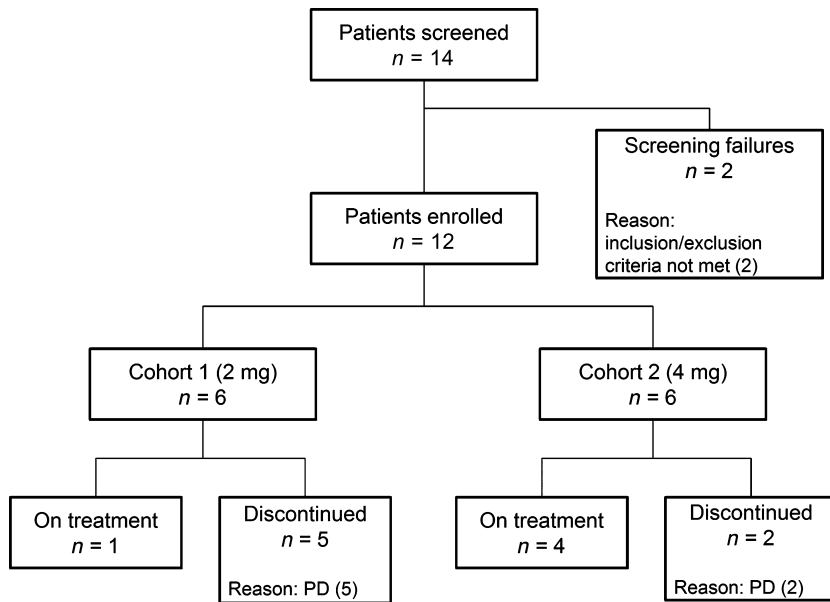


Fig. 2. Patient disposition for this phase 1, open-label, dose-escalation study that investigated the tolerated dose (recommended dose), safety, efficacy, and pharmacokinetics of pomalidomide alone or in combination with low-dose dexamethasone in Japanese patients with refractory or relapsed and refractory multiple myeloma. Data cut-off: November 19, 2013. PD, progressive disease.

progressed on treatment or died; median PFS was 5.1 months (95% confidence interval, 3.8 to not estimable). Two patients enrolled in Cohort 2 progressed on treatment

Table 2. Baseline demographics of Japanese patients with refractory or relapsed and refractory multiple myeloma (n = 12)

Characteristic, safety population	Cohort 1 (n = 6)	Cohort 2 (n = 6)	Overall (n = 12)
Median age, years (range)	67.5 (65–69)	69.0 (52–76)	68.0 (52–76)
Age, n (%)			
≤75 years	6 (100)	5 (83)	11 (92)
>75 years	0 (0)	1 (17)	1 (8)
Male, n (%)	3 (50)	4 (67)	7 (58)
Baseline CrCl, n (%)			
<45 mL/min	0 (0)	0 (0)	0 (0)
45 to < 60 mL/min	0 (0)	1 (17)	1 (8)
60 to < 80 mL/min	4 (67)	2 (33)	6 (50)
≥80 mL/min	2 (33)	3 (50)	5 (42)
Median time from first diagnosis, years (range)	6.00 (3.8–8.6)	4.20 (2.5–14.6)	5.15 (2.5–14.6)
MM stage, n (%)			
I	1 (17)	1 (17)	2 (17)
II	3 (50)	1 (17)	4 (33)
III	2 (33)	4 (67)	6 (50)
ECOG performance status, n (%)			
0	3 (50)	5 (83)	8 (67)
1	3 (50)	1 (17)	4 (33)
2	0 (0)	0 (0)	0 (0)
Median prior antineoplastic therapies, n (range)	6.5 (5–10)	5.5 (4–9)	6.0 (4–10)
Bortezomib	6 (100)	6 (100)	12 (100)
Dexamethasone	6 (100)	6 (100)	12 (100)
Lenalidomide	6 (100)	6 (100)	12 (100)
Thalidomide	3 (50)	3 (50)	6 (50)
Carfilzomib	2 (33)	0 (0)	2 (17)

CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; MM, multiple myeloma.

or died; median PFS has not been reached (95% confidence interval, 1.0 to not estimable).

Safety. The median treatment duration was 6.1 months in Cohort 1 and 5.6 months in Cohort 2; all patients except one received study treatment for ≥4.6 months. The median relative dose intensity of pomalidomide (dose intensity/planned dose intensity) was 1.0 and 0.89 for patients in Cohorts 1 and 2, respectively. During the study, no patients discontinued treatment due to AEs. Five patients had ≥1 dose reduction and 10 patients had ≥1 dose interruption. Overall, five patients experienced AEs leading to dose reductions in pomalidomide. Across all cohorts, grade ≥3 AEs occurred in 11 of 12 patients (92%). The most frequently occurring grade ≥3 AEs overall were neutropenia (67%), anemia (25%), lymphopenia (25%), and pneumonia (25%; Table 3). There were no reported incidences of deep vein thrombosis or pulmonary embolism of any grade; peripheral neuropathy occurred in one patient in each cohort, leading to dose interruption in one patient in Cohort 1. There

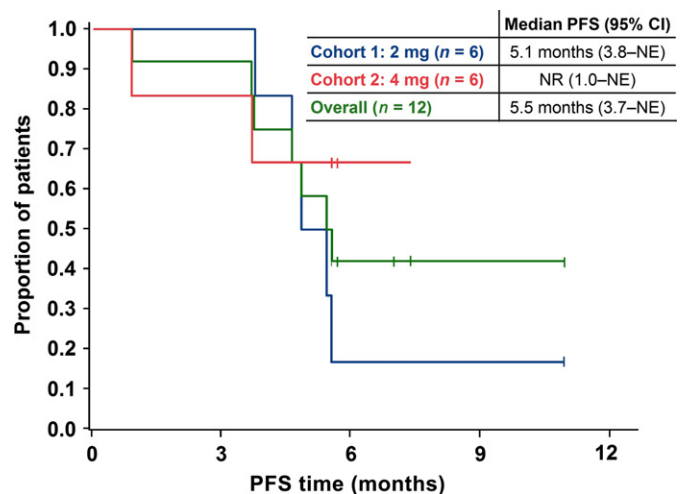


Fig. 3. Progression-free survival (PFS) in Japanese patients with refractory or relapsed and refractory multiple myeloma. CI, confidence interval; NE, not estimable; NR, not reached

Table 3. Treatment-emergent adverse events (TEAE) grade ≥ 3 occurring in two or more patients with refractory or relapsed and refractory multiple myeloma ($n = 12$)

System organ class/preferred term	Cohort 1	Cohort 2	Overall
	2 mg ($n = 6$)	4 mg ($n = 6$)	
Number of patients with ≥ 1 TEAE grade ≥ 3 , n (%)	5 (83)	6 (100)	11 (92)
Neutropenia	4 (67)	4 (67)	8 (67)
Anemia	1 (17)	2 (33)	3 (25)
Lymphopenia	2 (33)	1 (17)	3 (25)
Pneumonia	1 (17)	2 (33)	3 (25)
Leukopenia	2 (33)	0 (0)	2 (17)
Thrombocytopenia	2 (33)	0 (0)	2 (17)
Hypophosphatemia	1 (17)	1 (17)	2 (17)
Dyspnea	1 (17)	1 (17)	2 (17)

were no reported incidences of secondary primary malignancies during the trial.

Pharmacokinetics of pomalidomide. The PK parameters of pomalidomide are summarized in Table 4. The mean apparent clearance of drug from plasma, $t_{1/2}$, and apparent volume of distribution during the terminal phase were comparable at both dose levels. After treatment with a single 0.5-mg dose, the C_{max} of pomalidomide was 9.1 ng/mL (Fig. 4). The C_{max} values were 35.6 and 37.6 ng/mL for single or multiple doses of pomalidomide 2 mg, and 70.2 and 71.2 ng/mL after single or multiple doses of pomalidomide 4 mg respectively. The mean $AUC_{0-24 h}$ was 84.9 ng·h/mL after a single 0.5-mg dose of pomalidomide, 364.4 ng·h/mL and 411.5 ng·h/mL after single or multiple 2-

mg doses, and 685.7 ng·h/mL and 713.8 ng·h/mL after single or multiple 4-mg doses of pomalidomide, respectively. Statistical modeling was used to determine if pomalidomide exposure was proportional to the dose received. The slope derived from the power model of the measured exposure after single and multiple doses of pomalidomide was close to 1 (0.98–1.01 for single dose and 0.80–0.92 for multiple doses), indicating that pomalidomide showed dose proportionality.

Discussion

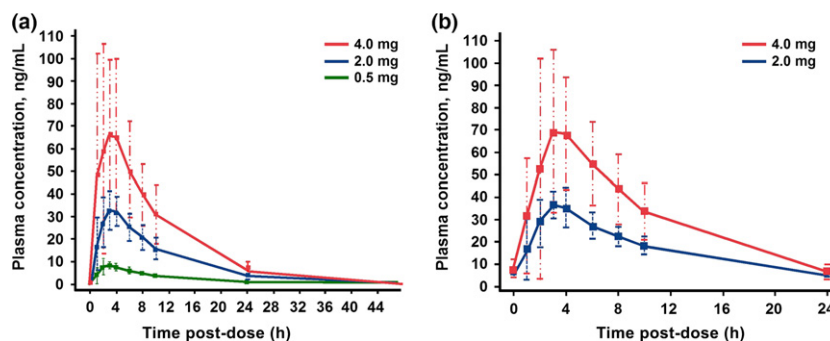
The TD (recommended dose) of pomalidomide observed in Japanese patients with RRMM was the same as that observed for white patients with RRMM in a phase 1 dose-finding study.⁽⁷⁾ Pomalidomide in combination with low-dose dexamethasone was tolerable at 4 mg, with an acceptable safety profile; patients should be monitored for AEs, and AEs should be managed appropriately. The safety profile observed in this study is consistent with AEs observed in prior studies of pomalidomide, in which neutropenia, anemia, and thrombocytopenia were the most frequently reported grade ≥ 3 AEs (53%, 21%, and 18%, respectively, in the phase 2 MM-002 trial and 48%, 33%, and 22%, respectively, in the phase 3 MM-003 trial).^(8,16) There were no new safety signals observed that might preclude the use of pomalidomide in this patient population.

The 40-mg weekly dose of dexamethasone was suitable. Of the 12 patients, four experienced at least one dose reduction of dexamethasone, five patients had at least one dose interruption, and the overall median relative dose intensity was 0.96. This dose of dexamethasone had not been rigorously assessed in Japanese patients prior to this study; however, it was decided

Table 4. Summary of pharmacokinetic (PK) parameters of pomalidomide in Japanese patients with refractory or relapsed and refractory multiple myeloma

PK parameter, mean (CV%)	Cohort 1 ($n = 6$)			Cohort 2 ($n = 6$)	
	Day -7 (0.5 mg)	Day 1 (2 mg)	Day 10 (2 mg)	Day 1 (4 mg)	Day 10 (4 mg)
C_{max} , ng/mL	9.1 (18.8)	35.6 (15.9)	37.6 (20.9)	70.2 (49.7)	71.2 (40.6)
$t_{1/2}$, h	6.4 (12.4)	6.9 (20.7)	7.3 (8.8)	6.0 (21.1)	5.5 (24.4)
$AUC_{0-24 h}$, ng·h/mL	84.9 (14.9)	364.4 (20.3)	411.5 (17.7)	685.7 (43.1)	713.8 (40.1)
CL/F, L/h	5.4 (14.6)	4.9 (26.4)	4.9 (17.7)	5.3 (44.8)	5.6 (40.1)
V_z/F , L	50 (18.5)	48.2 (15.9)	45.6 (15.4)	46 (37.4)	41.6 (42.0)

$AUC_{0-24 h}$, area under the plasma concentration–time curve from time 0 (dosing) to 24 h; CL/F, apparent clearance of drug from plasma; C_{max} , maximum plasma concentration; CV, coefficient of variation; PK, pharmacokinetic; $t_{1/2}$, estimated elimination half-life during terminal phase; V_z/F , apparent volume of distribution during the terminal phase.

Fig. 4. Plasma concentration of pomalidomide in Japanese patients with refractory or relapsed and refractory multiple myeloma after a single 0.5-mg dose, single or multiple 2-mg doses, or single or multiple 4-mg doses. Mean (\pm SD) plasma concentration shown. (a) —, 4.0 mg; —, 2.0 mg; —, 0.5 mg. (b) —, 4.0 mg; —, 2.0 mg.

that pomalidomide and dexamethasone would be coadministered because previous studies indicated that the combination creates a synergistic effect against MM. In non-clinical studies, pomalidomide in combination with dexamethasone showed greater antitumor activity than pomalidomide alone.^(17,18) Additionally, phase 2 of MM-002 examined the efficacy and safety of pomalidomide alone and in combination with low-dose dexamethasone in patients with RRMM who had been treated with bortezomib and lenalidomide.⁽⁹⁾ The results showed that the efficacy of pomalidomide was significantly enhanced by the addition of low-dose dexamethasone, with an acceptable safety profile.⁽⁹⁾ Thus, pomalidomide was coadministered with low-dose dexamethasone using the results of previous studies of pomalidomide as a guide.^(8,9)

The ORR (\geq PR) was 25% in the overall population (17% and 33% in Cohort 1 and Cohort 2, respectively). This is consistent with previous clinical observations of pomalidomide in heavily pretreated patients with RRMM. In the MM-002 trial, patients with RRMM with a median of five prior therapies treated with pomalidomide plus low-dose dexamethasone achieved an ORR of 33%.⁽⁹⁾ The ORR to treatment with pomalidomide plus low-dose dexamethasone was 31% in a large phase 3 trial of patients with RRMM with a median of five prior therapies (MM-003).⁽⁸⁾

Although an analysis of the effect of risk factors on efficacy was not a specified endpoint of this phase I study, and was therefore not carried out, previous studies of pomalidomide plus low-dose dexamethasone have evaluated this treatment in high-risk patients. The IFM 2009-02 trial reported that patients with del(17p) and/or t(4;14) cytogenetic abnormalities showed a shorter median PFS (2.6 months) and median OS (5.4 months) compared with the overall (intent-to-treat) ITT population (4.6 and 14.9 months, respectively).⁽¹⁰⁾ Median OS and PFS were similarly reduced in patients with high-risk cytogenetics compared with standard-risk patients in the MM-002 study (OS, 13.2 vs 21.7 months; PFS, 3.1 vs 5.5 months, respectively).⁽¹⁹⁾ However, a subanalysis of MM-003 revealed that, in patients treated with pomalidomide plus low-dose dexamethasone, PFS did not significantly differ between high- and standard-risk patients (3.8 vs 4.2 months, respectively; $P = 0.217$).

Interestingly, specific cytogenetic risks appear to have distinct impacts on treatment efficacy. It has been shown that patients with del(17p) experienced longer PFS⁽²⁰⁾ and OS^(20,21) than patients with t(4;14). In the IFM 2010-02 study of pomalidomide plus low-dose dexamethasone in patients with

adverse cytogenetics, the ORR in patients with del(17p) was more than twice that in patients with t(4;14) (32% vs 15%, respectively).⁽²¹⁾ The relationship between treatment efficacy and cytogenetic risk factors is a controversial topic that remains to be defined, and further investigation is required to determine how best to treat these high-risk patients.

Descriptive statistics and visual examination of the data revealed that systemic exposure of pomalidomide was proportional with the given dose, with limited dose accumulation after multiple doses. The PK parameters of pomalidomide in Japanese patients with RRMM are concordant with those of other studies of pomalidomide in patients with RRMM; one study reported a mean $t_{1/2}$ of 6.2–7.9 h across a range of pomalidomide doses (1, 2, 5, and 10 mg).⁽⁵⁾ Pomalidomide (at the TD of 4 mg) in combination with low-dose dexamethasone is being further investigated in Japanese patients with RRMM in a phase 2, multicenter, open-label trial (MM-011).⁽²²⁾

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Disclosure Statement

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