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Letter

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Letter

Isatuximab plus carfilzomib and dexamethasone in Japanese patients with relapsed multiple myeloma: subgroup analysis of the randomized, open label, phase 3 IKEMA study

Tadao Ishida[1], Shigeki Ito[2], Junji Tanaka[3], Michihiro Uchiyama[4], Yawara Kawano[5], Philippe Moreau[6], Thomas Martin[7], Marie-Laure Risse[8], Keisuke Tada[9], Kenshi Suzuki[10], and Kenichi Ishizawa[11,*]

[1]Department of Hematology, Japanese Red Cross Medical Center, Tokyo, Japan, [2]Division of Hematology & Oncology, Department of Internal Medicine, School of Medicine, Iwate Medical University, Yahaba, Japan, [3]Department of Hematology, Tokyo Women's Medical University, Tokyo, Japan, [4]Department of Hematology, Japanese Red Cross Society, Suwa Hospital, Suwa, Japan, [5]Department of Hematology, Kumamoto University Hospital, Kumamoto, Japan, [6]Department of Hematology, University Hospital of Nantes, Nantes, France, [7]Department of Medicine, University of California, San Francisco, CA, USA, [8]Sanofi, Research and Development, Vitry-Sur-Seine, France, [9]Sanofi, Research and Development, Tokyo, Japan, [10]Myeloma/Amyloidosis Center, Japanese Red Cross Medical Center, Tokyo, Japan and [11]Department of Internal Medicine III, Yamagata University Faculty of Medicine, Yamagata, Japan

*For reprints and all correspondence: Kenichi Ishizawa, Department of Internal Medicine III, Yamagata University Faculty of Medicine, 2-2-2 Iida-Nishi, Yamagata, Yamagata 990-9585, Japan. E-mail: kishizaw@med.id.yamagata-u.ac.jp

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Letter

To the Editor:

Multiple myeloma (MM) is the second most common hematological malignancy in adults, and although many new treatments are available, the disease remains incurable. Survival has improved with the availability of novel treatments, including immunomodulatory imide drugs (IMiDs, including thalidomide, lenalidomide and pomalidomide) and proteasome inhibitors (bortezomib, carfilzomib and ixazomib), but patients eventually become refractory and require additional therapies (1–3).

Isatuximab is an immunoglobulin G1 monoclonal antibody that binds to a specific epitope on the human cell surface antigen CD38, which is widely expressed on multiple myeloma (MM) cells (4–6), and acts through a number of mechanisms to produce antitumor activity (7–9). The combination of isatuximab plus carfilzomib-dexamethasone was investigated in the multinational, phase 3 IKEMA study (ClinicalTrials.gov identifier: NCT03275285) (10). Based on the results of this study, isatuximab plus carfilzomib-dexamethasone was approved in the US and Canada for the treatment of relapsed MM in patients who have received one to three prior lines of therapy, in the European Union for patients who have received at least one prior line of therapy, and in Japan for relapsed or refractory MM (11–15).

Here, we evaluated the efficacy and safety of isatuximab plus carfilzomib-dexamethasone in the subgroup of Japanese patients participating in IKEMA. The study design has been reported previously (10,16); briefly, patients who had received 1–3 prior lines of therapy were randomized 3:2 to receive isatuximab-carfilzomib-dexamethasone (isatuximab arm) or carfilzomib-dexamethasone (control arm). Isatuximab 10 mg/kg was administered weekly for 4 weeks, then every 2 weeks; patients in both treatment arms received the approved schedule of carfilzomib-dexamethasone until disease progression or unacceptable toxicity. The primary efficacy endpoint was progression-free survival (PFS) and key secondary efficacy endpoints included overall response, very good partial response (VGPR) or better, minimal residual disease negativity (MRD–) and complete response (CR) rates.

Between 15 November 2017 and 21 March 2019, 302 patients were randomized in the IKEMA study; of these, 19 were Japanese (7 in isatuximab arm, 12 in control arm). The demographics and clinical characteristics of these Japanese patients were well balanced between treatment arms at baseline. Patients were a median 64.0

Table 1. Summary of responses of Japanese people enrolled in the IKEMA study as per IRC

	Isatuximab + carfilzomib-dexamethasone ($n = 7$)	Control ($n = 12$)
Best overall response, *n* (%)		
sCR	0	0
CR	6 (85.7)	3 (25.0)
VGPR	0	4 (33.3)
PR	0	4 (33.3)
Minimal response	0	1 (8.3)
SD	1 (14.3)	0
ORR (sCR, CR, VGPR or PR), *n* (%)	6 (85.7)	11 (91.7)
95% CI	0.42–1.00	0.62–1.00
VGPR or better	6 (85.7)	7 (58.3)
95% CI	0.42–1.00	0.28–0.85
MRD negativity, *n* (%)	4 (57.1)	1 (8.3)
95% CI	0.18–0.90	0.00–0.38
sCR or CR, *n* (%)	6 (85.7)	3 (25.0)
95% CI	0.42–1.00	0.05–0.57
MRD negativity and sCR or CR, *n* (%)	4 (57.1)	0
95% CI	0.18–0.90	0.74–1.00

CI, confidence interval; CR, complete response; IRC, independent response committee; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

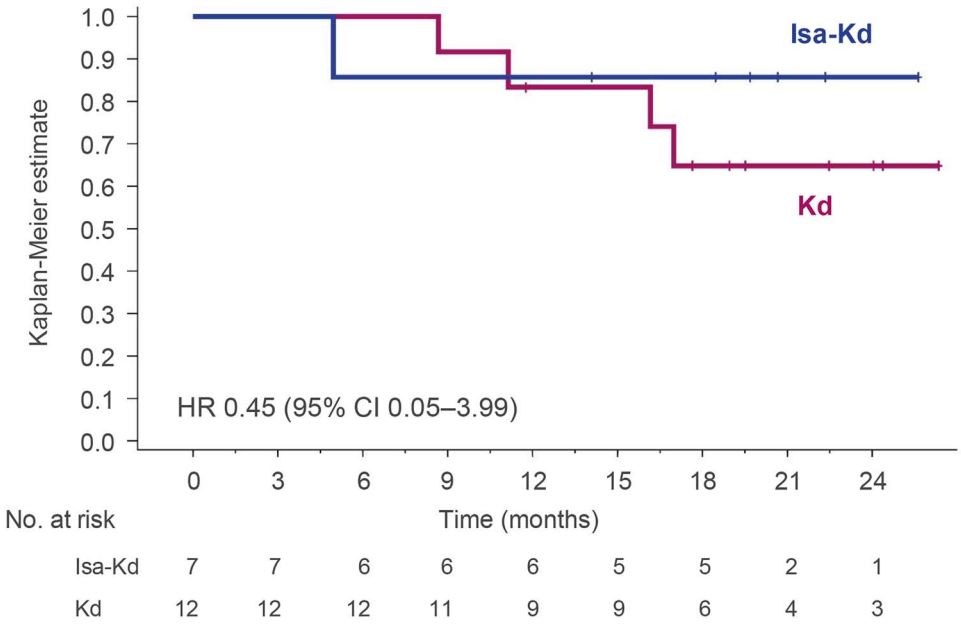

Figure 1. Kaplan–Meier analysis of progression-free survival among Japanese patients enrolled in the IKEMA study. CI, confidence interval; HR, hazard ratio; Isa, isatuximab; Kd, carfilzomib-dexamethasone.

(range 33–83) years old and had received a median of two prior lines of treatment.

At a median follow-up of 22.1 months, median PFS was not reached in either of the treatment arms (Fig. 1), giving a hazard ratio (HR) of 0.45 (95% confidence interval, 0.05–3.99) in favor of the isatuximab arm. Overall, six of seven patients receiving isatuximab had a CR and one had stable disease. In the control arm, three patients had CR, four had VGPR, four had partial response and one had a minimal response (Table 1). Therefore, the overall response rate was high in both treatment arms, but more patients in the isatuximab arm had a CR compared with patients in the control arm. In fact, all patients with an objective response in the isatuximab arm reached CR. The addition of isatuximab to carfilzomib-dexamethasone was also associated with an increase in the MRD– rate, and MRD– with stringent CR or CR was only reached in patients treated with isatuximab (Table 1).

Treatment-emergent adverse events (TEAEs) were generally manageable; there were no definitive discontinuations due to TEAEs and no deaths during study treatment in either study arm. No unexpected TEAEs were reported in the isatuximab arm. Grade ≥ 3 TEAEs occurred in 6 of 7 and 5 of 12 patients in the isatuximab and control arms, respectively, and three and four patients in the respective

groups reported serious TEAEs. Most frequent grade ≥ 3 TEAEs in the isatuximab versus the control arm were hypertension (two patients vs one patient, respectively) and pneumonia (two patients in each arm). Grade ≥ 3 TEAEs occurring only in the isatuximab arm were upper respiratory tract infection and pyrexia (each in 1 patient), while grade ≥ 3 insomnia occurred in two patients in the control arm. A higher incidence of grade 3 hematological laboratory abnormalities like anemia and neutropenia was seen in the isatuximab arm.

The main limitation of the present analysis is that it was conducted in a small subgroup of patients and therefore was not powered to detect a significant treatment difference in this subgroup. However, a consistent benefit was reported by the addition of isatuximab to either carfilzomib–dexamethasone or pomalidomide–dexamethasone in Asian patients. A post-marketing safety surveillance of isatuximab is planned in Japan, as the product has received Pharmaceutical and Medical Device Agency (PMDA) approval.

In conclusion, the PFS benefit of isatuximab in Japanese patients with relapsed MM was consistent with the results of the overall (10) and the East Asian (17) IKEMA study population, and patients in the isatuximab arm had a better quality of response to treatment than those in the control arm, as also observed in overall and East Asian patients. The safety profile was manageable with no unexpected TEAEs reported. Therefore, the addition of isatuximab to carfilzomib-dexamethasone is effective with a manageable safety profile in Japanese patients who have received 1–3 prior lines of therapy for relapsed MM.

Author contributions

MU, YK, PM, TM, MR, KS and KI contributed to study design. TI, SI, JT, MU, YK, PM, TM, MR, KS and KI contributed to data acquisition. TI, JT, MU, YK, PM, TM, MR, KT, KS and KI contributed to data analysis and interpretation of data. All authors critically reviewed the manuscript and approved the final draft for submission.

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Conflict of interest

Tadao Ishida has received honoraria from Ono Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Janssen Pharmaceutical K.K., Sanofi and Bristol-Myers Squibb K.K. Shigeki Ito has received honoraria from Bristol-Myers Squibb K.K., Celgene Corporation, Janssen Pharmaceutical K.K., Ono Pharmaceutical Co., Ltd., Sanofi and Takeda Pharmaceutical Co., Ltd. Yawara Kawano has received grants from the Kanae Foundation for the Promotion of Medical Science and the Shinnihon Foundation of Advanced Medical Treatment Research, and honoraria from Sanofi, Janssen Pharmaceutical K.K., Bristol-Myers Squibb K.K., Ono Pharmaceutical Co., Ltd. and Takeda Pharmaceutical Co., Ltd. Philippe Moreau has received consulting fees from AbbVie GK, Amgen K.K., Celgene Corporation, Janssen Pharmaceutical K.K. and Sanofi, and honoraria from AbbVie GK, Amgen K.K., Celgene Corporation, Janssen Pharmaceutical K.K. and Sanofi. Thomas Martin has received research funding from Sanofi, Janssen Pharmaceutical and Amgen, and consulting fees from GlaxoSmithKline. Marie-Laure Risse and Keisuke Tada are employees of Sanofi and may hold shares and/or stock options in the company. Kenshi Suzuki has received honoraria from Amgen K.K., AbbVie GK, Bristol-Myers Squibb K.K., Celgene Corporation, Janssen Pharmaceutical K.K., Novartis Pharma K.K., Ono Pharmaceutical Co., Ltd., Sanofi and Takeda Pharmaceutical Co., Ltd. Kenichi Ishizawa has received grants from Sanofi, IQVIA Solutions Japan K.K., Novartis Pharma K.K., AbbVie GK, Bayer Yakuhin, Ltd. and Otsuka Pharmaceutical Co., Ltd., and honoraria from Novartis Pharma K.K., Takeda Pharmaceutical Co., Ltd., Celbene Corporation, Ono Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., SRD, Merck Sharp & Dohme K.K., Micron, Inc., Janssen Pharmaceutical K.K. and Kyowa Kirin Co., Ltd. Junji Tanaka and Michihiro Uchiyama have no conflict to disclose.

Data availability

Qualified researchers can request access to patient-level data and related study documents including the clinical study report, study protocol with any amendments, blank case report forms, statistical analysis plan and dataset specifications. Patient-level data have been anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data-sharing criteria, eligible studies, and process for requesting access are at: https://www.vivli.org/.

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