ANTICANCER RESEARCH *43*: 157-165 (2023)
doi:10.21873/anticanres.16145

Measurable Residual Disease Assessment Using Next-Generation Flow in Patients With Relapsed and Refractory Multiple Myeloma Treated With a Combination of Carfilzomib, Lenalidomide, and Dexamethasone

TAKESHI YOROIDAKA[1,2], TAKESHI YAMASHITA[3], RYOICHI MURATA[3], KYOKO YOSHIHARA[4], SATOSHI YOSHIHARA[4], MIKIO UEDA[3], SHINJI NAKAO[1], KOSEI MATSUE[5] and HIROYUKI TAKAMATSU[1,6]

[1]Department of Hematology, Faculty of Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Ishikawa, Japan;
[2]Department of Hematology, Ishikawa Prefectural Central Hospital, Ishikawa, Japan;
[3]Department of Internal Medicine, Keiju Kanazawa Hospital, Ishikawa, Japan;
[4]Department of Hematology, Hyogo Medical University, Hyogo, Japan;
[5]Department of Hematology/Oncology, Kameda Medical Center, Chiba, Japan;
[6]Faculty of Transdisciplinary Sciences for Innovation, Institute of Transdisciplinary Sciences for Innovation, Kanazawa University, Ishikawa, Japan

Abstract. *Background/Aim: Carfilzomib, lenalidomide, and dexamethasone (KRD) therapy is widely used for patients with relapse/refractory multiple myeloma (RRMM). However, the response in patients who underwent assessment for measurable residual disease (MRD) has not been elucidated in a prospective study. We aimed to clarify the response rate and outcome of KRD therapy in patients in RRMM, including those with MRD. Patients and Methods: Twenty-one consecutive RRMM patients treated with KRD at 4 Japanese Centers between September 2016 and October 2018 were enrolled and assessed for MRD in the bone marrow (cut-off: 1×10^{-5}) using the EuroFlow-next-generation flow (NGF) method. Results: The median number of therapy lines before KRD was 3 (range=1-6), and the median number of KRD cycles was 4 (range=1-22). As the best overall response post-KRD therapy, 52% (11/21) of patients achieved a MRD negative complete response, 71% (15/21) achieved stringent complete response/ complete response, and 14% (3/21) achieved a very good partial response. MRD negativity was achieved in 12 of 16 (75%) and 14 of 21 (67%) patients during and after KRD treatment, respectively. The 2-year progression-free survival and overall survival from the start of KRD therapy were 100% and 100%, respectively, in MRD-positive cases and 88% and 100%, respectively, in MRD-negative cases (median follow-up=1.8 years). Grade 3/4 toxicities were reported in 15 patients (71%), with thrombocytopenia being the most frequent toxicity (6 patients, 29%). Conclusion: This is the first study that prospectively assessed MRD of patients with RRMM after KRD therapy. KRD treatment achieved a high MRD negativity rate and good outcomes with manageable toxicities.*

Correspondence to: Hiroyuki Takamatsu, MD, Ph.D., Department of Hematology, Faculty of Medicine, Institute of Medical, Pharmaceutical and Health Sciences/Faculty of Transdisciplinary Sciences for Innovation, Institute of Transdisciplinary Sciences for Innovation, Kanazawa University, 13-1 Takaramachi, Kanazawa, Ishikawa 920-8641, Japan. Tel: +81 762342275, Fax: +81 762344282, e-mail: takamaz@staff.kanazawa-u.ac.jp

Key Words: Multiple myeloma, next-generation flow, measurable residual disease, relapsed and refractory, carfilzomib, lenalidomide, dexamethasone (KRD).

Multiple myeloma (MM) is an incurable hematological malignancy, and obtaining a deep response is essential as it leads to prolonged progression-free survival (PFS) and overall survival (OS) (1). Methods for measuring measurable residual disease (MRD), such as next-generation flow (NGF) and next-generation sequencing (NGS), make it possible to stratify patients with complete response (CR) based on MRD levels, and novel agents increase the rate of CR and deeper responses (2-7).

Recently, a meta-analysis showed that MRD negativity was associated with significantly improved survival outcomes regardless of disease setting, MRD sensitivity

thresholds, cytogenetic risk, method of MRD assessment, and depth of clinical response at the time of MRD measurement (1, 7).

Carfilzomib is a next-generation proteasome inhibitor (PI) that functions as an irreversible inhibitor of the β5 chymotryptic subunit of the 20S proteasome. This new PI showed superior outcomes in relapse/refractory multiple myeloma (RRMM) patients in a head-to-head comparison between carfilzomib plus dexamethasone and bortezomib plus dexamethasone (8). Several phase 3 studies showed the clinical efficacy of three-drug regimens containing carfilzomib, such as carfilzomib plus lenalidomide plus dexamethasone (KRD), carfilzomib plus dexamethasone plus daratumumab, isatuximab plus pomalidomide plus dexamethasone, and carfilzomib plus pomalidomide plus dexamethasone for RRMM patients (5, 9-11). Though several studies assessed MRD after KRD treatment in newly diagnosed multiple myeloma (NDMM), to our knowledge, no study assessing MRD after KRD therapy in patients with RRMM has been conducted. Reports from patients with NDMM showed that approximately 60% achieved complete response (CR) or stringent CR and 56-62% achieved MRD negativity by multiparameter flow cytometry (12-14).

We hypothesized that deep response could predict better prognosis and, thus, we prospectively assessed the response of RRMM treated with KRD by NGF. This is the first study that prospectively assessed MRD of the patients with RRMM after KRD therapy.

Patients and Methods

Study design and subjects. This multicenter, open-label, prospective study was conducted at 4 Japanese Centers: the Kanazawa University, the Keiju Kanazawa Hospital, the Hyogo Medical University, and the Kameda Medical Center. Studies were conducted between September 2016 and October 2018. Both transplant-eligible and -ineligible patients with RRMM were enrolled to assess the response. All patients received the physician's choice of induction therapy and were treated with KRD after the diagnosis of RRMM. Patients with RRMM received KRD in 28-day cycles until disease progression or unacceptable toxicity. MM diagnosis was made according to the International Myeloma Working Group (IMWG) criteria (15) and response to therapy was assessed using the International Uniform Response Criteria (16). Stringent CR was defined as CR with normal free light chain ratio and absence of clonal cells in bone marrow (BM) biopsy by immunohistochemistry. Flow MRD-negative was defined as an MRD-negative status in a patient with CR. BM cells from 21 patients were analyzed using G-banding and FISH at diagnosis, and t(4;14), t(14;16), and/or del(17p13) were defined as high-risk chromosomal abnormalities by FISH. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (17). The study protocol was approved by the local ethics committees of Kanazawa University (No. 2016-125) and at each institute, and registered in the public clinical trial database (UMIN 000027259).

KRD treatment. Carfilzomib was administered intravenously on days 1, 2, 8, 9, 15, and 16. The dose was 20 mg/m^2 for days 1 and 2 of cycle 1, and 27 mg/m^2 thereafter. Lenalidomide was administered orally at 25 mg on days 1 to 21 of each cycle, and dexamethasone was administered orally or intravenously at 40 mg on days 1, 8, 15, and 22 of each cycle. Dose modification was permitted to manage toxicity.

Assessment of MRD. MRD was prospectively assessed in all patients using the EuroFlow-NGF method after KRD treatment. As part of routine clinical care, 2 ml of BM aspirate were collected and analyzed at the Kanazawa University (Kanazawa, Japan). The details of EuroFlow-NGF are described elsewhere (18). Briefly, the EuroFlow method uses ammonium chloride-based bulk lysis, followed by surface staining with antibodies against CD138-BV421, CD27-BV510, CD38 multi-epitope (ME)-FITC, CD56-PE, CD45-PerCP Cy5.5, CD19-PECy7, CD117-APC, and CD81-APC-C750 in tube 1, and surface/intracellular staining using antibodies against CD138-BV421, CD27-BV510, CD38 ME-FITC, CD56-PE, CD45-PerCP Cy5.5, CD19-PECy7, cytoplasmic (cy)Igκ-APC, and cyIgλ-APC-C750 after permeabilization in tube 2. An anti-CD38ME antibody was used to prevent the interference of anti-CD38 monoclonal antibodies, such as daratumumab. The FACSCanto™ II (BD Biosciences, Franklin Lakes, NJ, USA) flow cytometer was used to measure all samples, and gating and identification of clonal abnormal plasma cells were manually performed by experts using the Infinicyt software (Cytognos, Salamanca, Spain). The lower limit of MRD detection was set at 1×10^{-5}. Flow MRD-negativity was determined using the IMWG criteria (patients with CR or better and with at least 10^{-5} MRD negativity).

Statistical analyses. Baseline characteristics were reported descriptively, with continuous variables summarized as median and range. Response to therapy was defined in "Study design and subjects". The estimated OS and PFS were reported using the Kaplan-Meier method. All analyses were performed using GraphPad Prism version 9.3.1 (San Diego, CA, USA).

Results

Patient characteristics. A total of 21 patients were enrolled, and their responses were assessed between September 9, 2016, and October 16, 2018. The median patient age was 66 (range=30-83) years at the start of KRD treatment, the M-protein type was most commonly IgG in patients (71.4%), and 81.0% (17/21) of patients had International Staging System stage I or II disease. A total of 19% (4/21) of patients showed high-risk chromosomal abnormalities [del17p (n=3), t(14;16) (n=1)]. The median number of therapy lines before KRD was 3 (range=1-6), and the median number of KRD cycles was 4 (range=1-22). The median number of therapy lines after KRD was one (range=0-5) (Table I and Table II). The dose of KRD was not reduced in any patient due to adverse effect, but one patient (case 9) received an escalated dose of carfilzomib (36 mg/m^2) from cycle 2 because of insufficient response (19) after the approval of the Department of Hematology/Oncology at the Kameda Medical Center. The MRD of 15 patients after KRD treatment (median, 4 cycles) and 6 patients (cases 5, 7, 9, 10,

Table I. *Baseline characteristics*.

	n (%)
Total no. of patients	21
Age, median (range)	66 (30-83)
Sex (male/female)	12/9
M protein type	
IgG	15 (71.4)
IgA	3 (14.3)
Light chain	3 (14.3)
Light chain type	
Kappa/Lambda	14/7
ISS stage	
I	11 (52.4)
II	6 (28.6)
III	4 (19.0)
Number of regimens before KRD, median (range)	3 (1-6)
Prior therapies	
Bortezomib	21 (100)
Lenalidomide	19 (90.5)
Pomalidomide	3 (14.3)
Corticosteroid	21 (100.0)
Anthracycline	2 (9.5)
Alkylating reagent	16 (76.2)
Daratumumab	1 (4.8)
Auto-SCT	12 (57.1)
Number of KRD, median (range)	4 (1-22)
Number of regimens after KRD, median (range)	1 (0-5)
High-risk chromosomal abnormality* by FISH	4 (19.0)
Chromosome by G-banding	
Normal karyotype	18 (85.7)
Hyperdiploid	1 (4.8)
Non-hyperdiploid†	2 (9.5)

KRD, Carfilzomib plus lenalidomide plus dexamethasone; SCT, Stem-cell transplantation; *del(17p) (n=3), t(14;16) (n=1), †45,X,-Y (n=1), 46,XY,inv(9) (n=1).

16 and 21) after KRD therapy (median, 3 cycles) plus other regimens were assessed using NGF (Figure 1). After assessing the response to treatment, three patients (cases 2, 6, and 20) did not receive any subsequent therapy, 4 patients (cases 9, 14, 19, and 21) received autologous stem cell transplantation (ASCT), and 14 patients continued various treatments without ASCT (Table II).

KRD response. The rate of CR or better before KRD treatment was 9.5%, and the rate of a very good partial response (VGPR) or better was 42.8% (Figure 2). Two cases (case 12 and case 13) who had stringent CR before KRD therapy subsequently received KRD therapy because both cases remained MRD positive. Progressive disease (PD) and stable disease (SD) were reported in 14.3% (3/21) and 14.3% (3/21) of patients, respectively. The rate of CR or better after KRD therapy was 71.4% (15/21) and the rate of VGPR or better was 85.7% (18/21). Notably, the overall response rate was 100% and there was no PD or SD. The response was upgraded in 19 (90%) patients and maintained in two partial response (PR) cases (10%) after KRD treatment. After KRD therapy, MRD negativity was achieved in 67% (14/21) of patients (Figure 1). As the best overall response post-KRD treatment, 52% (11/21) of patients achieved Flow MRD-negative. Three of the four patients (cases 2, 4, and 11) with high-risk cytogenetics achieved Flow MRD-negative results after KRD treatment. Although one patient (case 9) remained PR status after KRD therapy, they achieved MRD negativity with subsequent therapy.

Outcomes. After a median follow-up of 21.0 months (range=5.0-30.0) post-KRD treatment, the estimated 2-year PFS rate from the start of KRD treatment was 95% and the 2-year OS rate was 100% (Figure 3). Among the 7 patients who were MRD-positive, the estimated 2-year PFS rate was 100%, and the 2-year OS rate was 100%. In contrast, the estimated 2-year PFS rate was 93%, and the 2-year OS rate was 100% among the 14 patients who were MRD-negative. Of note, case 6, who achieved MRD negativity and received no therapy, relapsed with bone-related extramedullary disease (EMD) adjacent to the thoracic spine (Figure 1).

Safety and tolerability. Table III summarizes the incidence of grade 3/4 AEs that occurred during KRD treatment. Fifteen (71%) patients reported grade 3/4 AEs. Grade 3/4 non-hematologic AEs included hypertension (14%), elevated liver function test results (14%), heart failure (5%), pneumonia (5%), sepsis (5%), fatigue (5%), and peripheral neuropathy (5%). Hematological grade 3/4 toxicities included thrombocytopenia (29%), lymphopenia (14%), and neutropenia (14%). Four grade 4 AEs were reported in two patients, including neutropenia and thrombocytopenia in one patient, and pneumonia and sepsis in the second patient. No grade 5 AEs or treatment-related deaths were reported throughout the treatment duration. Overall, KRD therapy was well tolerated, and all patients received at least one cycle of KRD with supportive measures.

Discussion

To the best of our knowledge, this is the first study to evaluate the response, including MRD, after KRD treatment in patients with RRMM. In this study, we demonstrated that KRD therapy can induce deep responses in patients with RRMM. Ninety percent of patients upgraded their response after KRD treatment, and 11/21 (52%) of patients achieved CR and MRD negativity (Flow MRD-negative). All patients, except one who relapsed with extramedullary disease, survived without progression during the follow-up period. The 2-year PFS and OS rates were 95% and 100%, respectively. Induction therapy with KRD and ASCT could induce 58-89% MRD negativity in NDMM patients (14, 20, 21), and KRD treatment for NDMM without intent for

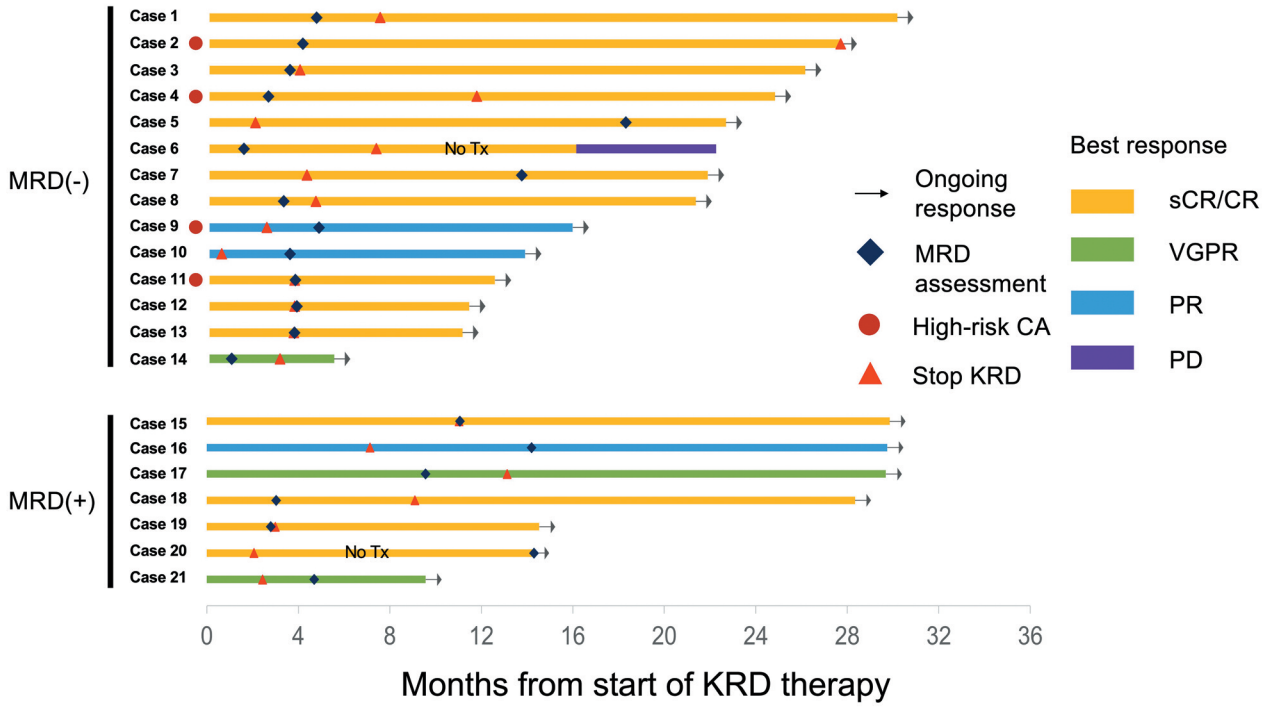

Figure 1. *Disease response and treatment status timelines. Each color bar shows the response after KRD treatment. Patients are grouped by their MRD status. The lower limit of MRD detection was set at* 1×10^{-5}. *KRD, Carfilzomib plus lenalidomide plus dexamethasone; MRD, measurable residual disease; CA, chromosomal abnormality; CR, complete response; PD, progressive disease; PR, partial response; sCR, stringent complete response; Tx, therapy; VGPR, very good partial response.*

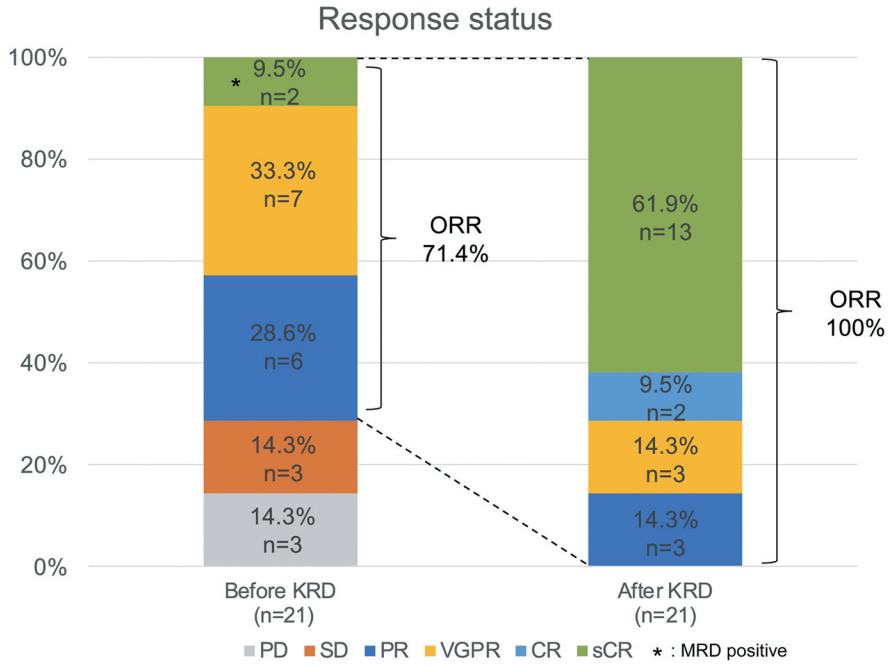

Figure 2. *Response rates before and after KRD therapy. The response rate was assessed in patients with RRMM before and after KRD treatment. Fifteen patients were assessed for response after KRD therapy (median 4 cycles), and 6 patients (cases 5, 7, 9, 10, 16, and 21) were assessed for response after KRD treatment (median 3 cycles) and other regimens. KRD, Carfilzomib plus lenalidomide plus dexamethasone; ORR, overall response rates; RRMM, relapse/refractory multiple myeloma.*

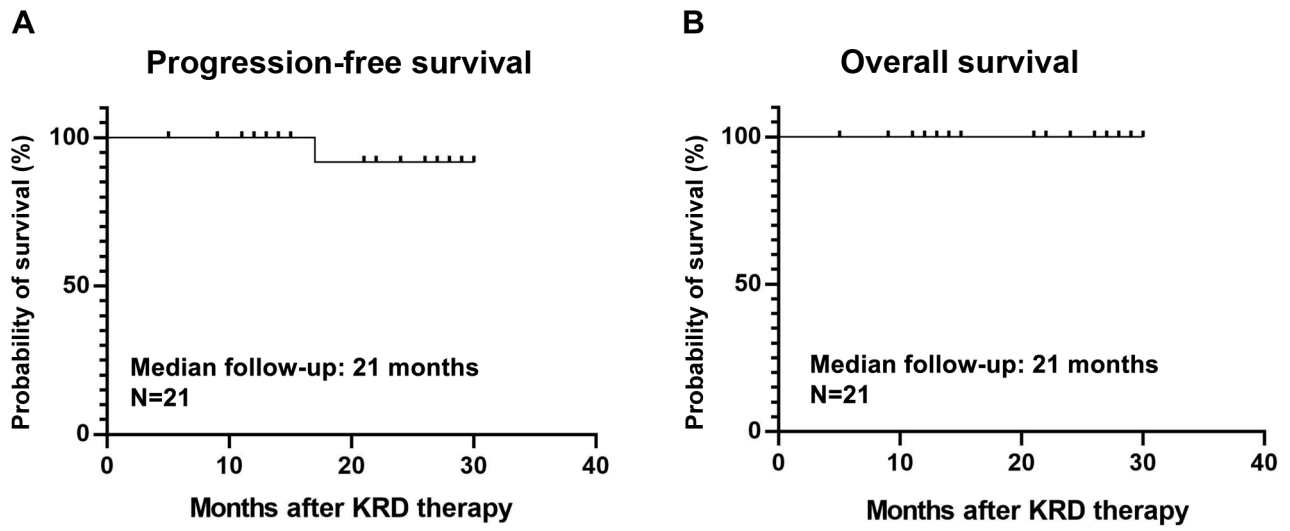

Figure 3. *Survival after KRD therapy. (A) Progression-free survival and (B) overall survival. Median follow-up: 21 months. KRD, Carfilzomib plus lenalidomide plus dexamethasone.*

immediate ASCT achieved 10% MRD negativity (4). Although no studies assessing MRD after KRD treatment in the refractory and relapse settings have been reported, several studies have reported that the rates of MRD negativity after treatment were 13-46% in patients with RRMM (22-24). Compared to these studies, the rate of MRD negativity was higher in our cohort. This could be partially due to the differences in the population and timing of KRD treatment. The median number of prior regimens was three, and 57% (12 of 21) of patients received ASCT before KRD therapy in this study. In patients who received ASCT before KRD therapy, the response assessment reflected the efficacy of both ASCT and KRD therapies, which could lead to overestimation of the better responses of KRD therapy. Most MRD-negative patients (93%, 13 of 14) showed no progression, but one patient relapsed with bone-related EMD after acquiring MRD-negativity and no treatment. The patient had skin lesions before KRD treatment. Paiva et al. reported that an analysis of patients with NDMM-registered in the PETHEMA/GEM2012MENOS65 trial showed that 7% of patients experienced disease progression despite undetectable MRD assessed by NGF. Most patients relapsed with extraosseous plasmacytomas, which were already observed at diagnosis (25). Because MRD assessment by NGF carries a risk of false-negative results in the presence of EMD, imaging studies, such as positron-emission tomography/computerized tomography and whole-body magnetic resonance imaging should be performed (25). All four patients who had high-risk cytogenetic abnormalities obtained MRD negativity after KRD treatment. Previous studies showed that the rate of MRD negativity was lower in patients with high-risk cytogenetics than in those with standard-risk cytogenetics; however, there was no difference in PFS and OS after acquiring MRD negativity (20, 26-28). However, whether KRD therapy could overcome the risk of high-risk cytogenetics is still controversial (14, 20). As shown for the daratumumab-combination regimens in patients with RRMM, the rates of patients who sustained MRD negativity for more than 12 months were lower in the high-risk cytogenetic group than in the standard-risk cytogenetic group (29), and this study suggested that a short follow-up period could lead to overestimation of the regimen when comparing the effectiveness of the cytogenetic risks.

In this study, 15 patients (71%) reported grade 3/4 AEs during KRD treatment. Major grade 3 non-hematological toxicities were hypertension (14%) and elevated liver function test (14%), and grade 3/4 thrombocytopenia (29%) was the most frequently observed hematological toxicity. The types of AEs were consistent with those previously reported and the rates of AEs were less frequent (10, 19). The reason for the low rates of grade 3/4 AEs could be the small number of KRD cycles in this study.

Our study has several limitations. First, the MRD of six patients (cases 5, 7, 9, 10, 16, and 21) was assessed after KRD and other therapy regimens, which could lead to the overestimation of KRD response. In fact, two patients (cases 9 and 10) received a daratumumab-containing regimen, and one patient (case 21) received ASCT, both of which could induce a high rate of undetectable MRD. Second, the median follow-up period (21 months) was relatively short, and we could not show a significant difference in outcomes between MRD-positive and MRD-negative patients.

Table II. *Cycles of KRD therapy before NGF.*

Case	Regimen before KRD therapy	Cycles of KRD and other regimen before NGF assessment	Regimen after KRD therapy	Total cycle of KRD
1	VMP	5	PomD	8
2	VD, VRD, KRD, C, ASCT, Allo-RIC	4	non	22
3	VD/VCD, V+C, VRD, tandem ASCT	4	R	4
4	VAD, C, tandem ASCT, VD, RD	3	R	11
5	VD, VRD, V+C, VRD, ASCT	3, IRD	IRD	3
6	VCD, C, ASCT, VTD, R	2	non	7
7	VRD, ASCT	4, R	R	4
8	VRD, KRD, C, KRD, ASCT	4	R, ERD	4
9	VRD	3, DaVD, C	DaVD, C, tandem ASCT, DaRD	3
10	VRD	1,DaVD	DaVD, DaVRD, V+C, DaRD, Pom	1
11	VRD, C+V, ASCT	4	R	4
12	VRD, KD, ASCT	5	IRD, R	5
13	VRD, C+V, ASCT	4	R	4
14	VRD	1	C, ASCT, IRD	2
15	TD, C, tandem ASCT, VD, RD, VRD	10	ERD	10
16	VCD, VTD, VRD, PomD, C, ASCT, VMP	8, ERD	ERD, DaVRD, DaVD, DaRD	8
17	VD, VMP, VRD, PomD	11	DaRD, DaVRD, DaRD	15
18	VCD+R, Pom, VMP	3	ERD	9
19	VRD	3	ASCT, DaRD	3
20	PAD, VRD	4	non	4
21*	VRD, DaVRD, DaVD, C+V, DaVD, DaRD	2, ASCT#1	ASCT#2, RD	2

KRD, Carfilzomib plus lenalidomide plus dexamethasone; NGF, next-generation flow; V, bortezomib; D, dexamethasone; M, melphalan; P, prednisone; R, lenalidomide; Pom, pomalidomide; T, thalidomide; C, cyclophosphamide; ASCT, autologous stem cell transplantation; PAD, bortezomib, doxorubicin, high-dose dexamethasone; Da, daratumumab; VAD, vincristine, doxorubicin, dexamethasone; K, carfilzomib; Allo-RIC, allogeneic transplantation with dose-reduced intensity conditioning; E, elotuzumab; I, ixazomib.*Case 21 received tandem ASCT after KRD.

Novel drugs and combinations have made it possible to achieve good responses and MRD negativity even in RRMM (5, 11, 30, 31). In the CANDOR trial (Dara-KD *vs*. KD), 12.5% of patients with RRMM achieved Flow MRD-negative status, and no patients progressed to disease during the follow-up period. Similarly, 20% of patients with RRMM who received isatuximab-KD achieved Flow MRD-negative results in the IKEMA trial. This suggests that novel drugs and their combinations have a great impact on MRD status and outcomes in patients with RRMM.

In conclusion, these data suggest that KRD therapy has the potential to induce deeper response and lead to good outcomes, even in patients with RRMM. KRD treatment also demonstrated favorable tolerability and safety profiles. Further studies are needed to confirm the long-term efficacy and safety of KRD therapy in RRMM patients.

Table III. *Grade 3/4 adverse events.*

	n (%)
Nonhematologic	
Hypertension	3 (14)
Elevated liver function test	3 (14)
Heart failure	1 (5)
Pneumonia	1 (5)
Sepsis	1 (5)
Fatigue	1 (5)
Peripheral neuropathy	1 (5)
Hematologic	
Thrombocytopenia	6 (29)
Lymphopenia	3 (14)
Neutropenia	3 (14)

Conflicts of Interest

This work was supported by Ono Pharmaceutical Co., Ltd. HT received honoraria from Bristol-Myers Squibb company and Ono Pharmaceutical Co., Ltd. SY received honoraria from Bristol-Myers Squibb company and Ono Pharmaceutical Co., Ltd. The rest of Authors do not have any relationships to disclose.

Authors' Contributions

T. Yoroidaka, T. Yamashita, R.M., K.Y., S.Y., and H.T. collected clinical data and blood samples. T.Y. and H.T. performed flow cytometry experiments and analyzed data. H.T. designed the research. T.Y. and H.T. wrote the manuscript. All Authors critically reviewed the manuscript and checked the final version.

Acknowledgements

The Authors thank the patients and their physicians for contributing to this study.

References

1 Munshi NC, Avet-Loiseau H, Anderson KC, Neri P, Paiva B, Samur M, Dimopoulos M, Kulakova M, Lam A, Hashim M, He J, Heeg B, Ukropec J, Vermeulen J, Cote S and Bahlis N: A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma. Blood Adv *4(23)*: 5988-5999, 2020. PMID: 33284948. DOI: 10.1182/bloodadvances.2020002827

2 Facon T, Kumar SK, Plesner T, Orlowski RZ, Moreau P, Bahlis N, Basu S, Nahi H, Hulin C, Quach H, Goldschmidt H, O'Dwyer M, Perrot A, Venner CP, Weisel K, Mace JR, Raje N, Tiab M, Macro M, Frenzel L, Leleu X, Ahmadi T, Wang J, Van Rampelbergh R, Uhlar CM, Tromp B, Delioukina M, Vermeulen J and Usmani SZ: Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol *22(11)*: 1582-1596, 2021. PMID: 34655533. DOI: 10.1016/S1470-2045(21)00466-6

3 Mateos MV, Cavo M, Blade J, Dimopoulos MA, Suzuki K, Jakubowiak A, Knop S, Doyen C, Lucio P, Nagy Z, Pour L, Cook M, Grosicki S, Crepaldi A, Liberati AM, Campbell P, Shelekhova T, Yoon SS, Iosava G, Fujisaki T, Garg M, Krevvata M, Chen Y, Wang J, Kudva A, Ukropec J, Wroblewski S, Qi M, Kobos R and San-Miguel J: Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. Lancet *395(10218)*: 132-141, 2020. PMID: 31836199. DOI: 10.1016/S0140-6736(19)32956-3

4 Kumar SK, Jacobus SJ, Cohen AD, Weiss M, Callander N, Singh AK, Parker TL, Menter A, Yang X, Parsons B, Kumar P, Kapoor P, Rosenberg A, Zonder JA, Faber E Jr, Lonial S, Anderson KC, Richardson PG, Orlowski RZ, Wagner LI and Rajkumar SV: Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol *21(10)*: 1317-1330, 2020. PMID: 32866432. DOI: 10.1016/S1470-2045(20)30452-6

5 Dimopoulos M, Quach H, Mateos MV, Landgren O, Leleu X, Siegel D, Weisel K, Yang H, Klippel Z, Zahlten-Kumeli A and Usmani SZ: Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. Lancet *396(10245)*: 186-197, 2020. PMID: 32682484. DOI: 10.1016/S0140-6736(20)30734-0

6 Lahuerta JJ, Paiva B, Vidriales MB, Cordón L, Cedena MT, Puig N, Martinez-Lopez J, Rosiñol L, Gutierrez NC, Martín-Ramos ML, Oriol A, Teruel AI, Echeveste MA, de Paz R, de Arriba F, Hernandez MT, Palomera L, Martinez R, Martin A, Alegre A, De la Rubia J, Orfao A, Mateos MV, Blade J, San-Miguel JF and GEM (Grupo Español de Mieloma)/PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatías Malignas) Cooperative Study Group: Depth of response in multiple myeloma: a pooled analysis of three PETHEMA/GEM clinical trials. J Clin Oncol *35(25)*: 2900-2910, 2017. PMID: 28498784. DOI: 10.1200/JCO.2016.69.2517

7 Landgren O, Devlin S, Boulad M and Mailankody S: Role of MRD status in relation to clinical outcomes in newly diagnosed multiple myeloma patients: a meta-analysis. Bone Marrow Transplant *51(12)*: 1565-1568, 2016. PMID: 27595280. DOI: 10.1038/bmt.2016.222

8 Dimopoulos MA, Moreau P, Palumbo A, Joshua D, Pour L, Hájek R, Facon T, Ludwig H, Oriol A, Goldschmidt H, Rosiñol L, Straub J, Suvorov A, Araujo C, Rimashevskaya E, Pika T, Gaidano G, Weisel K, Goranova-Marinova V, Schwarer A, Minuk L, Masszi T, Karamanesht I, Offidani M, Hungria V, Spencer A, Orlowski RZ, Gillenwater HH, Mohamed N, Feng S, Chng WJ and ENDEAVOR Investigators: Carfilzomib and dexamethasone *versus* bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol *17(1)*: 27-38, 2016. PMID: 26671818. DOI: 10.1016/S1470-2045(15)00464-7

9 Mehta P, Yadav N, Bhaarat M, Mirgh S, Khushoo V, Thekuddan S, Agrawal N, Ahmed R and Bhurani D: Carfilzomib-Pomalidomide-Dexamethasone (KPD) in relapsed/refractory multiple myeloma patients - an institutional retrospective analysis. Blood *134(Suppl_1)*: 5572-5572, 2019. DOI: 10.1182/blood-2019-131674

10 Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Špička I, Oriol A, Hájek R, Rosiñol L, Siegel DS, Mihaylov GG, Goranova-Marinova V, Rajnics P, Suvorov A, Niesvizky R, Jakubowiak AJ, San-Miguel JF, Ludwig H, Wang M, Maisnar V, Minarik J, Bensinger WI, Mateos MV, Ben-Yehuda D, Kukreti V, Zojwalla N, Tonda ME, Yang X, Xing B, Moreau P, Palumbo A and ASPIRE Investigators: Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med *372(2)*: 142-152, 2015. PMID: 25482145. DOI: 10.1056/NEJMoa1411321

11 Moreau P, Dimopoulos MA, Mikhael J, Yong K, Capra M, Facon T, Hajek R, Špička I, Baker R, Kim K, Martinez G, Min CK, Pour L, Leleu X, Oriol A, Koh Y, Suzuki K, Risse ML, Asset G, Macé S, Martin T and IKEMA study group: Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. Lancet *397(10292)*: 2361-2371, 2021. PMID: 34097854. DOI: 10.1016/S0140-6736(21)00592-4

12 Gay F, Musto P, Rota-Scalabrini D, Bertamini L, Belotti A, Galli M, Offidani M, Zamagni E, Ledda A, Grasso M, Ballanti S, Spadano A, Cea M, Patriarca F, D'Agostino M, Capra A, Giuliani N, de Fabritiis P, Aquino S, Palmas A, Gamberi B, Zambello R, Petrucci MT, Corradini P, Cavo M and Boccadoro M: Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): a randomised, open-label, phase 2 trial. Lancet Oncol *22(12)*: 1705-1720, 2021. PMID: 34774221. DOI: 10.1016/S1470-2045(21)00535-0

13 Korde N, Roschewski M, Zingone A, Kwok M, Manasanch EE, Bhutani M, Tageja N, Kazandjian D, Mailankody S, Wu P,

Morrison C, Costello R, Zhang Y, Burton D, Mulquin M, Zuchlinski D, Lamping L, Carpenter A, Wall Y, Carter G, Cunningham SC, Gounden V, Sissung TM, Peer C, Maric I, Calvo KR, Braylan R, Yuan C, Stetler-Stevenson M, Arthur DC, Kong KA, Weng L, Faham M, Lindenberg L, Kurdziel K, Choyke P, Steinberg SM, Figg W and Landgren O: Treatment with carfilzomib-lenalidomide-dexamethasone with lenalidomide extension in patients with smoldering or newly diagnosed multiple myeloma. JAMA Oncol *1(6)*: 746-754, 2015. PMID: 26181891. DOI: 10.1001/jamaoncol.2015.2010

14 Kazandjian D, Korde N, Mailankody S, Hill E, Figg WD, Roschewski M and Landgren O: Remission and progression-free survival in patients with newly diagnosed multiple myeloma treated with carfilzomib, lenalidomide, and dexamethasone: five-year follow-up of a phase 2 clinical trial. JAMA Oncol *4(12)*: 1781-1783, 2018. PMID: 30477009. DOI: 10.1001/jamaoncol.2018.5457

15 Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, Kumar S, Hillengass J, Kastritis E, Richardson P, Landgren O, Paiva B, Dispenzieri A, Weiss B, LeLeu X, Zweegman S, Lonial S, Rosinol L, Zamagni E, Jagannath S, Sezer O, Kristinsson SY, Caers J, Usmani SZ, Lahuerta JJ, Johnsen HE, Beksac M, Cavo M, Goldschmidt H, Terpos E, Kyle RA, Anderson KC, Durie BG and Miguel JF: International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol *15(12)*: e538-e548, 2014. PMID: 25439696. DOI: 10.1016/S1470-2045(14)70442-5

16 Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, Munshi N, Lonial S, Bladé J, Mateos MV, Dimopoulos M, Kastritis E, Boccadoro M, Orlowski R, Goldschmidt H, Spencer A, Hou J, Chng WJ, Usmani SZ, Zamagni E, Shimizu K, Jagannath S, Johnsen HE, Terpos E, Reiman A, Kyle RA, Sonneveld P, Richardson PG, McCarthy P, Ludwig H, Chen W, Cavo M, Harousseau JL, Lentzsch S, Hillengass J, Palumbo A, Orfao A, Rajkumar SV, Miguel JS and Avet-Loiseau H: International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol *17(8)*: e328-e346, 2016. PMID: 27511158. DOI: 10.1016/S1470-2045(16)30206-6

17 US Department of Health and Human Services NIoH, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0, 2017. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf [Last accessed on November 21, 2022]

18 Flores-Montero J, Sanoja-Flores L, Paiva B, Puig N, García-Sánchez O, Böttcher S, van der Velden VHJ, Pérez-Morán JJ, Vidriales MB, García-Sanz R, Jimenez C, González M, Martínez-López J, Corral-Mateos A, Grigore GE, Fluxá R, Pontes R, Caetano J, Sedek L, Del Cañizo MC, Bladé J, Lahuerta JJ, Aguilar C, Bárez A, García-Mateo A, Labrador J, Leoz P, Aguilera-Sanz C, San-Miguel J, Mateos MV, Durie B, van Dongen JJM and Orfao A: Next Generation Flow for highly sensitive and standardized detection of minimal residual disease in multiple myeloma. Leukemia *31(10)*: 2094-2103, 2017. PMID: 28104919. DOI: 10.1038/leu.2017.29

19 Jakubowiak AJ, Dytfeld D, Griffith KA, Lebovic D, Vesole DH, Jagannath S, Al-Zoubi A, Anderson T, Nordgren B, Detweiler-Short K, Stockerl-Goldstein K, Ahmed A, Jobkar T, Durecki DE, McDonnell K, Mietzel M, Couriel D, Kaminski M and Vij R: A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. Blood *120(9)*: 1801-1809, 2012. PMID: 22665938. DOI: 10.1182/blood-2012-04-422683

20 Jasielec JK, Kubicki T, Raje N, Vij R, Reece D, Berdeja J, Derman BA, Rosenbaum CA, Richardson P, Gurbuxani S, Major S, Wolfe B, Stefka AT, Stephens L, Tinari KM, Hycner T, Rojek AE, Dytfeld D, Griffith KA, Zimmerman TM and Jakubowiak AJ: Carfilzomib, lenalidomide, and dexamethasone plus transplant in newly diagnosed multiple myeloma. Blood *136(22)*: 2513-2523, 2020. PMID: 32735641. DOI: 10.1182/blood.2020007522

21 Gay F, Cerrato C, Petrucci M, Zambello R, Gamberi B, Ballanti S, Omedè P, Palmieri S, Troia R, Spada S, Gozzetti A, Caravita T, Spadano A, Palumbo A, Montefusco V, Musto P, Cavo M and Boccadoro M: Efficacy of carfilzomib lenalidomide dexamethasone (KRd) with or without transplantation in newly diagnosed myeloma according to risk status: Results from the FORTE trial. Journal of Clinical Oncology *37(15_suppl)*: 8002-8002, 2020. DOI: 10.1200/JCO.2019.37.15_suppl.8002

22 Dimopoulos MA, San-Miguel J, Belch A, White D, Benboubker L, Cook G, Leiba M, Morton J, Ho PJ, Kim K, Takezako N, Moreau P, Kaufman JL, Sutherland HJ, Lalancette M, Magen H, Iida S, Kim JS, Prince HM, Cochrane T, Oriol A, Bahlis NJ, Chari A, O'Rourke L, Wu K, Schecter JM, Casneuf T, Chiu C, Soong D, Sasser AK, Khokhar NZ, Avet-Loiseau H and Usmani SZ: Daratumumab plus lenalidomide and dexamethasone *versus* lenalidomide and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of POLLUX. Haematologica *103(12)*: 2088-2096, 2018. PMID: 30237262. DOI: 10.3324/haematol.2018.194282

23 Paiva B, Chandia M, Puig N, Vidriales MB, Perez JJ, Lopez-Corral L, Ocio EM, Garcia-Sanz R, Gutierrez NC, Jimenez-Ubieto A, Lahuerta JJ, Mateos MV and San Miguel JF: The prognostic value of multiparameter flow cytometry minimal residual disease assessment in relapsed multiple myeloma. Haematologica *100(2)*: e53-e55, 2015. PMID: 25381128. DOI: 10.3324/haematol.2014.115162

24 Spencer A, Lentzsch S, Weisel K, Avet-Loiseau H, Mark TM, Spicka I, Masszi T, Lauri B, Levin MD, Bosi A, Hungria V, Cavo M, Lee JJ, Nooka AK, Quach H, Lee C, Barreto W, Corradini P, Min CK, Scott EC, Chanan-Khan AA, Horvath N, Capra M, Beksac M, Ovilla R, Jo JC, Shin HJ, Sonneveld P, Soong D, Casneuf T, Chiu C, Amin H, Qi M, Thiyagarajah P, Sasser AK, Schecter JM and Mateos MV: Daratumumab plus bortezomib and dexamethasone *versus* bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR. Haematologica *103(12)*: 2079-2087, 2018. PMID: 30237264. DOI: 10.3324/haematol.2018.194118

25 Paiva B, Puig N, Cedena MT, Rosiñol L, Cordón L, Vidriales MB, Burgos L, Flores-Montero J, Sanoja-Flores L, Lopez-Anglada L, Maldonado R, de la Cruz J, Gutierrez NC, Calasanz MJ, Martin-Ramos ML, Garcia-Sanz R, Martinez-Lopez J, Oriol A, Blanchard MJ, Rios R, Martin J, Martinez-Martinez R, Sureda A, Hernandez MT, de la Rubia J, Krsnik I, Moraleda JM, Palomera L, Bargay J, Van Dongen JJM, Orfao A, Mateos MV, Blade J, San-Miguel JF, Lahuerta JJ and GEM (Grupo Español de Mieloma)/PETHEMA (Programa Para el Estudio de la Terapéutica en Hemopatías Malignas) Cooperative Study Group: Measurable residual disease by next-generation flow cytometry in multiple myeloma. J Clin Oncol *38(8)*: 784-792, 2020. PMID: 31770060. DOI: 10.1200/JCO.19.01231

26 Perrot A, Lauwers-Cances V, Corre J, Robillard N, Hulin C, Chretien ML, Dejoie T, Maheo S, Stoppa AM, Pegourie B, Karlin L, Garderet L, Arnulf B, Doyen C, Meuleman N, Royer B, Eveillard JR, Benboubker L, Dib M, Decaux O, Jaccard A, Belhadj K, Brechignac S, Kolb B, Fohrer C, Mohty M, Macro M, Richardson PG, Carlton V, Moorhead M, Willis T, Faham M, Anderson KC, Harousseau JL, Leleu X, Facon T, Moreau P, Attal M, Avet-Loiseau H and Munshi N: Minimal residual disease negativity using deep sequencing is a major prognostic factor in multiple myeloma. Blood *132(23)*: 2456-2464, 2018. PMID: 30249784. DOI: 10.1182/blood-2018-06-858613

27 Goicoechea I, Puig N, Cedena MT, Burgos L, Cordón L, Vidriales MB, Flores-Montero J, Gutierrez NC, Calasanz MJ, Ramos MM, Lara-Astiaso D, Vilas-Zornoza A, Alignani D, Rodriguez I, Sarvide S, Alameda D, Garcés JJ, Rodriguez S, Fresquet V, Celay J, Garcia-Sanz R, Martinez-Lopez J, Oriol A, Rios R, Martin-Sanchez J, Martinez-Martinez R, Sarra J, Hernandez MT, de la Rubia J, Krsnik I, Moraleda JM, Palomera L, Bargay J, Martinez-Climent JA, Orfao A, Rosiñol L, Mateos MV, Lahuerta JJ, Blade J, San Miguel J and Paiva B: Deep MRD profiling defines outcome and unveils different modes of treatment resistance in standard- and high-risk myeloma. Blood *137(1)*: 49-60, 2021. PMID: 32693406. DOI: 10.1182/blood.2020006731

28 San-Miguel J, Avet-Loiseau H, Paiva B, Kumar S, Dimopoulos MA, Facon T, Mateos MV, Touzeau C, Jakubowiak A, Usmani SZ, Cook G, Cavo M, Quach H, Ukropec J, Ramaswami P, Pei H, Qi M, Sun S, Wang J, Krevvata M, DeAngelis N, Heuck C, Van Rampelbergh R, Kudva A, Kobos R, Qi M and Bahlis NJ: Sustained minimal residual disease negativity in newly diagnosed multiple myeloma and the impact of daratumumab in MAIA and ALCYONE. Blood *139(4)*: 492-501, 2022. PMID: 34269818. DOI: 10.1182/blood.2020010439

29 Avet-Loiseau H, San-Miguel J, Casneuf T, Iida S, Lonial S, Usmani SZ, Spencer A, Moreau P, Plesner T, Weisel K, Ukropec J, Chiu C, Trivedi S, Amin H, Krevvata M, Ramaswami P, Qin X, Qi M, Sun S, Qi M, Kobos R and Bahlis NJ: Evaluation of sustained minimal residual disease negativity with daratumumab-combination regimens in relapsed and/or refractory multiple myeloma: analysis of POLLUX and CASTOR. J Clin Oncol *39(10)*: 1139-1149, 2021. PMID: 33513030. DOI: 10.1200/JCO.20.01814

30 Siegel DS, Schiller GJ, Samaras C, Sebag M, Berdeja J, Ganguly S, Matous J, Song K, Seet CS, Talamo G, Acosta-Rivera M, Bar M, Quick D, Anz B, Fonseca G, Reece D, Pierceall WE, Chung W, Zafar F, Agarwal A and Bahlis NJ: Pomalidomide, dexamethasone, and daratumumab in relapsed refractory multiple myeloma after lenalidomide treatment. Leukemia *34(12)*: 3286-3297, 2020. PMID: 32376855. DOI: 10.1038/s41375-020-0813-1

31 Attal M, Richardson PG, Rajkumar SV, San-Miguel J, Beksac M, Spicka I, Leleu X, Schjesvold F, Moreau P, Dimopoulos MA, Huang JS, Minarik J, Cavo M, Prince HM, Macé S, Corzo KP, Campana F, Le-Guennec S, Dubin F, Anderson KC and ICARIA-MM study group: Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. Lancet *394(10214)*: 2096-2107, 2019. PMID: 31735560. DOI: 10.1016/S0140-6736(19)32556-5

Received October 21, 2022
Revised November 8, 2022
Accepted November 21, 2022