Daratumumab-resistant multiple myeloma with extramedullary disease successfully treated with combination elotuzumab, pomalidomide and dexamethasone: A case report

MASATAKA SAKASHITA[1], NAOHI SAHARA[1], JUN AOKI[1], TAKASHI MATSUNAGA[1], SEIICHIRO KOBAYASHI[1], SHINSUKE KITAHARA[1,2], TOMOKI FUJII[1,2] and NOBUHIRO OHNO[1]

Departments of [1]Hematology and [2]Clinical Oncology, Kanto Rosai Hospital, Kawasaki, Kanagawa 211-0021, Japan

Received November 12, 2023; Accepted January 23, 2024

DOI: 10.3892/ol.2024.14381

Abstract. Despite the emergence of monoclonal antibodies, the prognosis of patients with multiple myeloma (MM) with extramedullary disease remains poor. The present report describes a rare case of daratumumab-refractory MM that was successfully treated with elotuzumab, pomalidomide and dexamethasone. A 66-year-old male patient diagnosed with MM was treated with bortezomib, lenalidomide and dexamethasone, followed by high-dose chemotherapy and autologous stem cell transplantation. Thereafter, the patient was treated with lenalidomide and dexamethasone as maintenance therapy. This was changed to daratumumab, bortezomib and dexamethasone when new paraskeletal lesions were identified, resulting in marked tumor shrinkage. After 15 months, an increase in serum monoclonal protein levels, development of a skeletal lesion in the right second rib and extramedullary disease of the right thoracic mediastinal lymph nodes were noted. Treatment with elotuzumab, pomalidomide and dexamethasone (EPd) resulted in expeditious symptomatic improvement and regression of the lesions. Notably, during daratumumab, bortezomib and dexamethasone treatment, lymphocyte counts gradually increased to a level at which elotuzumab was sufficiently effective. EPd might be a promising strategy for the treatment of patients with relapsed extramedullary MM while on daratumumab treatment.

Correspondence to: Dr Naohi Sahara, Department of Hematology, Kanto Rosai Hospital, 1-1 Kizukisumiyoshicho, Nakahara, Kawasaki, Kanagawa 211-0021, Japan
E-mail: saharan@kantoh.johas.go.jp

Abbreviations: MM, multiple myeloma; NK, natural killer; mAbs, monoclonal antibodies; SLAMF7, signaling lymphocytic activation molecule family member 7; IgG, immunoglobulin G; CT, computed tomography; ADCC, antigen-dependent cellular cytotoxicity; EPd, elotuzumab, pomalidomide and dexamethasone; DBd, daratumumab, bortezomib and dexamethasone

Key words: elotuzumab, MM, extramedullary disease, daratumumab, NK cells

Introduction

Multiple myeloma (MM) is a mature B-cell neoplasm characterized by the presence of clonal plasma cells in bone marrow. Extramedullary MM is associated with aggressive disease and poor prognosis owing to its increased proliferation and therapeutic resistance (1). Although the emergence of monoclonal antibodies (mAbs), such as daratumumab, elotuzumab, and isatuximab, has dramatically improved the prognosis of MM, the optimal sequence of treatment regimens remains controversial (2).

Daratumumab, an anti-CD38 antibody, reduces the number of natural killer (NK) cells, requiring more than six months for recovery (3). Another monoclonal antibody, elotuzumab, is an anti-signaling lymphocytic activation molecule family member 7 (SLAMF7) antibody that activates NK cells (4,5). Several studies have shown that pre-treatment with daratumumab attenuates the effectiveness of elotuzumab (6,7). To date, there have been no reports discussing the use of different mAbs for MM associated with extramedullary disease. Herein, we report a unique case of daratumumab-resistant MM with extramedullary disease that was successfully treated with elotuzumab, pomalidomide, and dexamethasone (EPd).

Case report

A 66-year-old Japanese male with a history of hypertension, dyslipidemia, and type 2 diabetes was referred to our hospital for multiple osteolytic tumors of the skull, ribs, and ilium. Laboratory tests revealed anemia (hemoglobin, 12.1 g/dl) and increased immunoglobulin G (IgG, 2,866 mg/dl). Serum levels of β_2 microglobulin and lactate dehydrogenase (LDH) were 3.4 mg/l and 182 U/l, respectively. Immunoelectrophoresis demonstrated the presence of monoclonal component IgG κ-type. Urinary Bence Jones protein was not detected. Serum free light chain κ level was 12.2 mg/l; λ level, 3.1 mg/l; and κ/λ ratio, 3.94. Bone marrow aspirate showed 52% infiltration of monoclonal plasma cells. Cytogenetic analysis

revealed a normal male karyotype (Fig. 1A) and fluorescence *in situ* hybridization (FISH) was negative for del(17p), t(4;14) (Fig. 1B). FISH for t(14;16) was also negative, but gain/amp(1q21) was not tested. The patient was diagnosed with stage II MM according to the Revised International Staging System (8).

Treatment with four cycles of bortezomib, lenalidomide, and dexamethasone, followed by autologous stem cell transplantation resulted in a very good partial response according to the 2016 International Myeloma Working Group uniform response criteria (9). Thereafter, maintenance therapy was continued with lenalidomide and dexamethasone. Thirty-four months later, although the IgG level was well controlled (548 mg/dl), anterior thoracic pain developed. Computed tomography (CT) revealed new osteolytic lesions in the sternum; therefore, the treatment was changed to daratumumab, bortezomib, and dexamethasone (DBd) at 16 mg/kg on days 1, 8, and 15; 1.3 mg per square of body-surface area twice weekly for two weeks; and 20 mg on the day of and the day after bortezomib, respectively (10), resulting in alleviation of his pain and tumor shrinkage.

Fifteen months after the initiation of DBd, severe right-sided chest pain developed, and the IgG level was elevated to 2,266 mg/dl. The lymphocyte count was elevated to 3,072/μl (Fig. 2). Lymphocytes were morphologically normal, while neither lymphocytes subset analysis nor NK cell activity was performed. Serum β_2 microglobulin and κ/λ ratio were 4.5 mg/dl and 0.80, respectively. Chest radiography revealed a massive tumor occupying the apex of the right lung (Fig. 1C). A chest CT scan showed a bulky tumor arising from the right rib, extending to the right thorax, and pleural dissemination with lymph node metastasis to the right axilla and mediastinum (Fig. 1D). Neither bone marrow examination including FISH analysis nor biopsy of extramedullary mass was performed due to the patient's refusal. Upon clinical relapse of MM with extramedullary disease, the treatment was changed to EPd (elotuzumab, 10 mg/kg on days 1, 8, 15 and 22 during cycles 1 and 2, and 20 mg/kg on day 1 of each cycle thereafter; pomalidomide, 4 mg per day on days 1 through 21; dexamethasone, 40 mg once weekly) (11), which resulted in expeditious resolution of the chest pain. Notably, chest radiography on day 13 of treatment revealed marked regression of the tumor in the right apex (Fig. 1E), and serum IgG levels rapidly decreased to 492 mg/dl (Fig. 2). Three months after the initiation of EPd, a subsequent CT scan demonstrated disappearance of the disease (Fig. 1F).

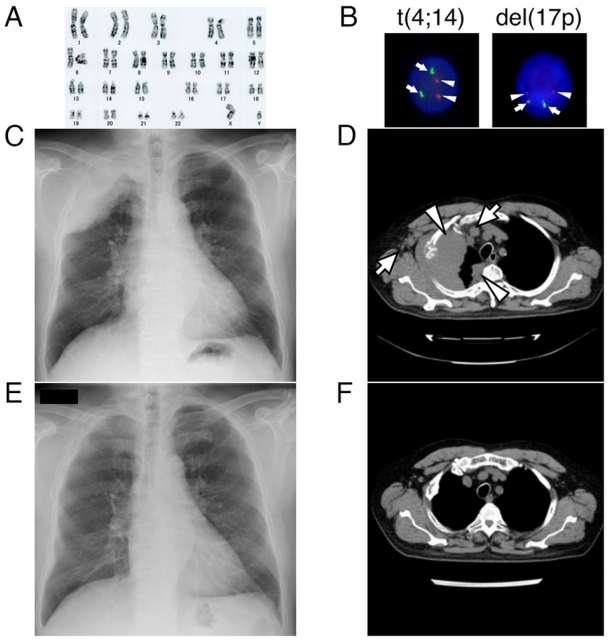

Figure 1. Results of karyotyping and FISH analysis, and radiographic images. (A) Cytogenetic analysis showing normal male karyotype (46, XY). (B) FISH analysis showing no signal for t(4;14) and del(17p). For t(4;14), the red signal (arrowheads) indicates *FGFR* and the green signal (arrows) indicates *IGH*. For del(17p), the red signal (arrowheads) indicates *TP53* and the green signal (arrows) indicates *D17Z1* (magnification, x500). (C) Chest radiograph showing a massive tumor occupying the right apex. (D) Chest CT showing a bulky tumor extending to the right thorax with pleural dissemination (arrowheads). Lymph node metastases to the right axilla and mediastinum were also noted (arrows). (E) Chest radiograph on day 13 of EPd, showing marked regression of the tumor. (F) Chest CT 3 months after the initiation of EPd showing disappearance of the disease. CT, computed tomography; del, deletion; EPd, elotuzumab, pomalidomide and dexamethasone; FISH, fluorescence *in situ* hybridization.

Discussion

Even in the era of monoclonal antibodies and proteasome inhibitors, the prognosis in MM with extramedullary disease still remains poor (12,13). In a retrospective study assessing elotuzumab-based regimens for the treatment of extramedullary MM, progression-free survival and overall survival were short (3.8 and 12.9 months, respectively) (14). Here, we present the first case of DBd-resistant MM with extramedullary disease that was successfully treated with EPd.

The mechanism of action of elotuzumab depends on the action of NK cells. Elotuzumab binds to SLAMF7, which is expressed at high levels in both MM and NK cells, and exerts cytotoxic effects by activating NK cells and antibody-dependent cellular cytotoxicity (ADCC) (4,5). In contrast, daratumumab, an anti-CD38 antibody, reduces the NK cell count in peripheral blood mononuclear cells by binding to CD38 expressed on NK cells (15). It takes six months for NK cells to recover in number after cessation of daratumumab infusion (3). These results suggest that continuous elotuzumab may have weakened effects when used following treatment with daratumumab.

Hoylman *et al* (6) compared clinical outcomes in patients who received either daratumumab before elotuzumab (dara-first) or elotzumab before daratumumab (elo-first) and demonstrated that the response rate to elotuzumab was diminished in the dara-first group, with a significantly longer cumulative progression free survival in the elo-first group. In randomized phase III studies, daratumumab was more effective against relapsed/refractory MM when administered with fewer prior lines of therapy (10,16-18). Furthermore, in transplant-ineligible newly diagnosed MM, the ALCYONE and MAIA studies showed that treatment with daratumumab as a front-line therapy produced superior outcomes (19-22). Based on these results, daratumumab

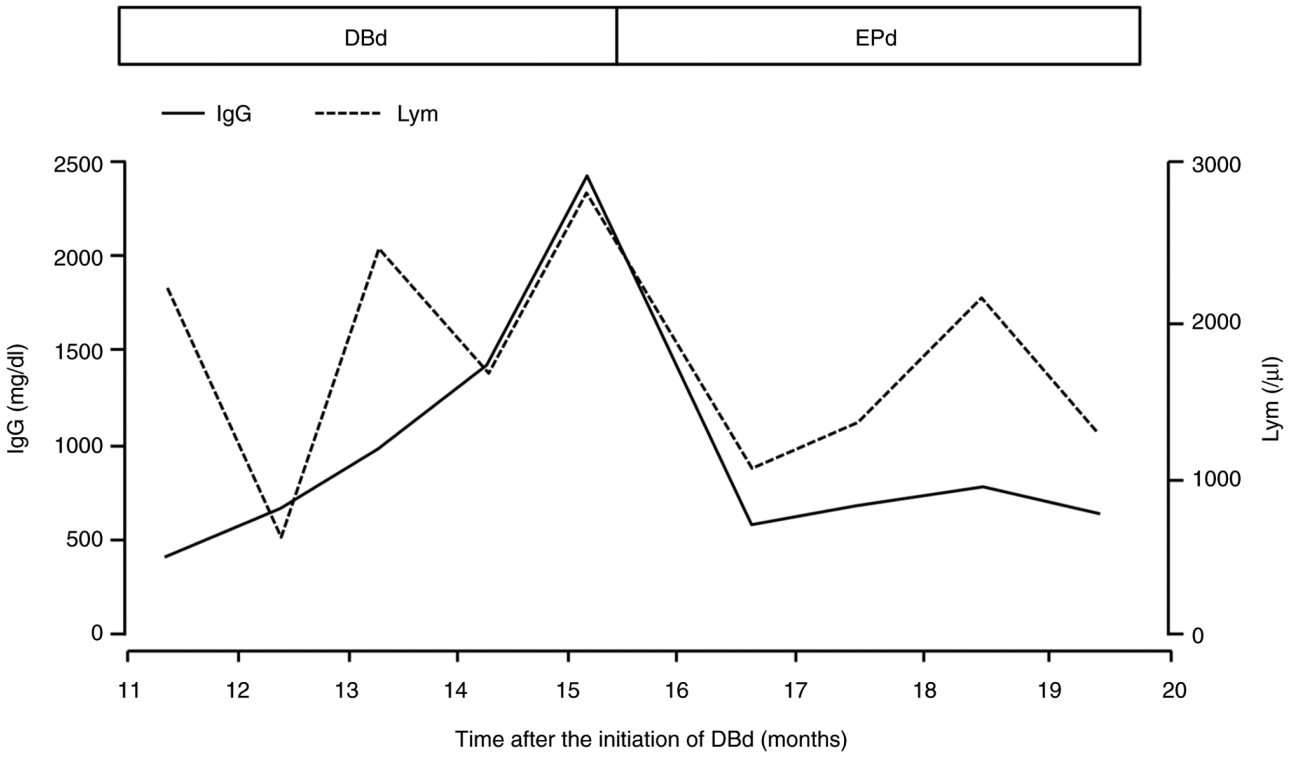

Figure 2. Clinical course of the presented case. DBd, daratumumab, bortezomib and dexamethasone; EPd, elotuzumab, pomalidomide and dexamethasone; IgG, immunoglobulin G; Lym, lymphocytes.

is likely to be administered before elotuzumab, and an approach that allows retention of elotuzumab's efficacy is required.

Disease burden, NK cell count, and SLAMF7 expression in myeloma cells have been suggested as biomarkers of elotuzumab response (23). However, these markers are not readily measurable in clinical settings. Recently, a simpler clinical index has been reported to predict response to elotuzumab treatment. This report showed that the median time to next treatment was significantly longer in patients with higher lymphocyte counts (>1,400/μl), non-deviated κ/λ ratio (0.1-10), lower β_2 microglobulin (<5.5 mg/l), and no prior daratumumab use (7). In the present case, although elotuzumab was administered immediately after daratumumab treatment, the patient responded well. Interestingly, in the present case, the lymphocyte counts during DBd gradually increased to a level at which elotuzumab was sufficiently effective (Fig. 2). Although the NK cell fraction was not measured in the present case, the increase in lymphocytes during DBd may reflect the existence of abundant NK cells. Furthermore, in a mouse model, DBd treatment enhanced the cytotoxicity of expanded NK cells by upregulating the expression of NK cell-activating ligands, downregulating the expression of NK cell-inhibitory ligands, and promoting ADCC (24). The augmentation of NK cell cytotoxicity by DBd may also contribute to the enhanced therapeutic effect of EPd. On the other hand, elotuzumab has been shown to inhibit myeloma cell growth *in vivo* through antibody-dependent cellular phagocytosis by macrophages (25,26). This mechanism of action of elotuzumab may have contributed to the dramatic response seen in our case.

Overall, the findings in our case suggest that EPd might be a promising strategy for the treatment of patients with relapsed extramedullary MM while on daratumumab treatment. Further studies are required to select a more appropriate sequence of treatment for these patients.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MS, NS and SKo conceived and designed the study. MS, NS, JA, TM, SKo, SKi, TF and NO acquired, analyzed and interpreted the data. MS and NS drafted and revised the manuscript, and confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of case details and associated images.

Competing interests

The authors declare that they have no competing interests.

References

1. Bladé J, Beksac M, Caers J, Jurczyszyn A, von Lilienfeld-Toal M, Moreau P, Rasche L, Rosiñol L, Usmani SZ, Zamagni E and Richardson P: Extramedullary disease in multiple myeloma: A systematic literature review. Blood Cancer J 12: 45, 2022.
2. Laubach JP, van de Donk N, Davies FE and Mikhael J: Practical considerations for antibodies in myeloma. Am Soc Clin Oncol Educ Book 38: 667-674, 2018.
3. Casneuf T, Xu XS, Adams HC III, Axel AE, Chiu C, Khan I, Ahmadi T, Yan X, Lonial S, Plesner T, *et al*: Effects of daratumumab on natural killer cells and impact on clinical outcomes in relapsed or refractory multiple myeloma. Blood Adv 24: 2105-2114, 2017.
4. His ED, Steinle R, Balasa B, Szmania S, Draksharapu A, Shum BP, Huseni M, Powers D, Nanisetti A, Zhang Y, *et al*: CS1, a potential new therapeutic antibody target for the treatment of multiple myeloma. Clin Cancer Res 14: 2775-2784, 2008.
5. Tai YT, Dillon M, Song W, Leiba M, Li XF, Burger P, Lee AI, Podar K, Hideshima T, Rice AG, *et al*: Anti-CS1 humanized monoclonal antibody HuLuc63 inhibits myeloma cell adhesion and induces antibody-dependent cellular cytotoxicity in the bone marrow milieu. Blood 112: 1329-1337, 2008.
6. Hoylman E, Brown A, Perissinotti AJ, Marini BL, Pianko M, Ye JC, Campagnaro E and Nachar VR: Optimal sequence of daratumumab and elotuzumab in relapsed and refractory multiple myeloma. Leuk Lymphoma 61: 691-698, 2020.
7. Shimazu Y, Kanda J, Kosugi S, Ito T, Kaneko H, Imada K, Shimura Y, Fuchida SI, Fukushima K, Tanaka H, *et al*: Efficacy of elotuzumab for multiple myeloma in reference to lymphocyte counts and kappa/lambda ratio or B2 microglobulin. Sci Rep 13: 5159, 2023.
8. Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, Richardson P, Caltagirone S, Lahuerta JJ, Facon T, *et al*: Revised International Staging System for multiple myeloma: A report from International Myeloma Working Group. J Clin Oncol 33: 2863-2869, 2015.
9. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, Munshi N, Lonial S, Bladé J, Mateos MV, *et al*: International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 17: e328-e346, 2016.
10. Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, Spicka I, Hungria V, Munder M, Mateos MV, *et al*: Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med 375: 754-766, 2016.
11. Dimopoulos MA, Dytfeld D, Grosicki S, Moreau P, Takezako N, Hori M, Leleu X, LeBlanc R, Suzuki K, Raab MS, *et al*: Elotuzumab plus pomalidomide and dexamethasone for multiple myeloma. N Engl J Med 379: 1811-1822, 2018.
12. Badar T, Srour S, Bashir Q, Shah N, Al-Atrash G, Hosing C, Popat U, Nieto Y, Orlowski RZ, Champlin R and Qazilbash MH: Predictors of inferior clinical outcome in patients with standard-risk multiple myeloma. Eur J Haematol 98: 263-268, 2017.
13. Rasche L, Bernard C, Topp MS, Kapp M, Duell J, Wesemeier C, Haralambieva E, Maeder U, Einsele H and Knop S: Features of extramedullary myeloma relapse: High proliferation, minimal marrow involvement, adverse cytogenetics: A retrospective single-center study of 24 cases. Ann Hematol 91: 1031-1037, 2012.
14. Danhof S, Rasche L, Mottok A, Steinmüller T, Zhou X, Schreder M, Kilian T, Strifler S, Rosenwald A, Hudecek M, *et al*: Elotuzumab for the treatment of extramedullary myeloma: A retrospective analysis of clinical efficacy and SLAMF7 expression patterns. Ann Hematol 100: 1537-1546, 2021.
15. Krejcik J, Casneuf T, Nijhof IS, Verbist B, Bald J, Plesner T, Syed K, Liu K, van de Donk NW, Weiss BM, *et al*: Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. Blood 128: 384-394, 2016.
16. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, Rabin N, Orlowski RZ, Komarnicki M, Suzuki K, *et al*: Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 375: 1319-1331, 2016.
17. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, Rabin N, Orlowski RZ, Suzuki K, Plesner T, *et al*: Overall survival with daratumumab, lenalidomide, and dexamethasone in previously treated multiple myeloma (POLLUX): A randomized, open-label, phase III trial. J Clin Oncol 41: 1590-1599, 2023.
18. Sonneveld P, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, Spicka I, Hungria V, Munder M, Mateos MV, *et al*: Overall survival with daratumumab, bortezomib, and dexamethasone in previously treated multiple myeloma (CASTOR): A randomized, open-label, phase III trial. J Clin Oncol 41: 1600-1609, 2023.
19. Mateos MV, Dimopoulos MA, Cavo M, Suzuki K, Jakubowiak A, Knop S, Doyen C, Lucio P, Nagy Z, Kaplan P, *et al*: Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. N Engl J Med 378: 518-528, 2018.
20. Mateos MV, Cavo M, Blade J, Dimopoulos MA, Suzuki K, Jakubowiak A, Knop S, Doyen C, Lucio P, Nagy Z, *et al*: Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): A randomised, open-label, phase 3 trial. Lancet 395: 132-141, 2020.
21. Facon T, Kumar S, Plesner T, Orlowski RZ, Moreau P, Bahlis N, Basu S, Nahi H, Hulin C, Quach H, *et al*: Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. N Engl J Med 380: 2104-2115, 2019.
22. Facon T, Kumar SK, Plesner T, Orlowski RZ, Moreau P, Bahlis N, Basu S, Nahi H, Hulin C, Quach H, *et al*: 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: 1582-1596, 2021.
23. Danhof S, Strifler S, Hose D, Kortüm M, Bittrich M, Hefner J, Einsele H, Knop S and Schreder M: Clinical and biological characteristics of myeloma patients influence response to elotuzumab combination therapy. J Cancer Res Clin Oncol 145: 561-571, 2019.
24. Thangaraj JL, Ahn SY, Jung SH, Vo MC, Chu TH, Thi Phan MT, Kwon M, Lee KH, Kim M, Song GY, *et al*: Expanded natural killer cells augment the antimyeloma effect of daratumumab, bortezomib, and dexamethasone in a mouse model. Cell Mol Immunol 18: 1652-1661, 2021.
25. Kurdi AT, Glavey SV, Bezman NA, Jhatakia A, Guerriero JL, Manier S, Moschetta M, Mishima Y, Roccaro A, Detappe A, *et al*: Antibody-dependent cellular phagocytosis by macrophages is a novel mechanism of action of elotuzumab. Mol Cancer Ther 17: 1454-1463, 2018.
26. Dimopoulos MA, Dytfeld D, Grosicki S, Moreau P, Takezako N, Hori M, Leleu X, LeBlanc R, Suzuki K, Raab MS, *et al*: Elotuzumab plus pomalidomide and dexamethasone for relapsed/refractory multiple myeloma: Final overall survival analysis from the randomized phase II ELOQUENT-3 trial. J Clin Oncol 41: 568-578, 2023.