



Title	Effects of prior osteoporosis treatment on the treatment response of romosozumab followed by denosumab in patients with postmenopausal osteoporosis
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1 **Short Communication**
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6 3 Effects of prior osteoporosis treatment on the treatment response of romosozumab followed
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8 4 by denosumab in patients with postmenopausal osteoporosis
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15 6 **Authors**
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17
18 7 Kosuke Ebina, MD, PhD ^{1, 2),*}, Yuki Etani, MD, PhD ²⁾, Hideki Tsuboi, MD, PhD ³⁾, Yoshio
19
20 8 Nagayama, MD ⁴⁾, Masafumi Kashii, MD, PhD ⁵⁾, Akira Miyama, MD, PhD ⁶⁾, Yasuo
21
22 9 Kunugiza, MD, PhD ⁷⁾, Makoto Hirao, MD, PhD ²⁾, Gensuke Okamura, MD, PhD ³⁾, Takaaki
23
24
25 10 Noguchi, MD, PhD ⁸⁾, Kenji Takami, MD ²⁾, Atsushi Goshima, MD ²⁾, Taihei Miura, MD ²⁾,
26
27 11 Yuji Fukuda, MD ²⁾, Takuya Kurihara, MD ²⁾, Seiji Okada, MD, PhD ²⁾, and Ken Nakata,
28
29
30 12 MD, PhD ⁹⁾
31
32
33 13
34
35
36 14 **Affiliations**
37
38
39 15 ¹⁾ Department of Musculoskeletal Regenerative Medicine, Osaka University, Graduate
40
41 16 School of Medicine, 2-2 Yamada-oka, Suita, Osaka 565-0871, Japan
42
43
44 17 ²⁾ Department of Orthopaedic Surgery, Osaka University Graduate School of Medicine, 2-2
45
46
47 18 Yamada-oka, Suita, Osaka 565-0871, Japan
48
49
50 19 ³⁾ Department of Orthopaedic Surgery, Osaka Rosai Hospital, 1179-3 Nagasone-cho, Kita-ku,
51
52 20 Sakai 591-8025, Japan
53
54
55 21 ⁴⁾ Nagayama Rheumatology and Orthopaedic Clinic, 4-3-25 Hiokisounishi-machi, Higashi-
56
57
58 22 ku, Sakai 599-8114, Japan
59
60
61
62
63
64
65

23 ⁵⁾ Department of Orthopaedic Surgery, Toyonaka Municipal Hospital, 4-14-1 Shibahara-cho,

1 24 Toyonaka, Osaka 560-8565, Japan

2 3 4 5 ⁶⁾ Department of Orthopaedic Surgery, Osaka Toneyama Medical Center, 5-1-1 Toneyama,

6 7 8 25 Toyonaka, Osaka 560-8552, Japan

9 10 11 27 ⁷⁾ Department of Orthopaedic Surgery, Japan Community Health care Organization,

12 13 28 Hoshigaoka Medical Center, 4-8-1 Hoshigaoka, Hirakata, Osaka, 573-8511, Japan

14 15 29 ⁸⁾ Department of Orthopaedic Surgery, National Hospital Organization Osaka Minami

16 17 30 Medical Center, 2-1 Kidohigashi, Kawachinagano, Osaka, 586-8521, Japan

18 19 31 ⁹⁾ Department of Health and Sport Sciences, Osaka University Graduate School of Medicine,

20 21 32 2-2 Yamada-oka, Suita, Osaka 565-0871, Japan

22 23 33

24 25 34 ***Corresponding author:**

26 27 35 Phone: +81-6-6210-8439; Fax: +81-6-6210-8438

28 29 36 E-mail: k-ebina@ort.med.osaka-u.ac.jp

30 31 37

32 33 38 **ORCIDs**

34 35 39 Kosuke Ebina: 0000-0002-2426-1024

36 37 40 Makoto Hirao: 0000-0002-1408-7851

38 39 41 Ken Nakata: 0000-0002-8964-4229

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52 **Abstract**

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2 53 *Purpose:*

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6 54 To investigate the effects of prior osteoporosis treatment on the response to treatment with
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8 55 romosozumab (ROMO) followed by denosumab (DMAb) in patients with postmenopausal
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11 56 osteoporosis.

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13 57 *Methods:*

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17 58 In this prospective, observational, multicenter study, treatment naïve patients (Naïve; n = 55)
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19 59 or patients previously treated with bisphosphonates (BP; n = 37), DMAb (DMAb; n = 45), or
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21
22 60 teriparatide (TPTD; n = 17) (mean age, 74.6 years; T-scores of the lumbar spine [LS] -3.2
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24 61 and total hip [TH] -2.6) were switched to ROMO for 12 months, followed by DMAb for 12
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26 62 months. Bone mineral density (BMD) and serum bone turnover markers were evaluated for
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28 63 24 months.

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30 64 *Results:*

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33 65 BMD increase was observed at 12 and 24 months in the following patients: Naïve (18.2% and
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35 66 22.0%), BP (10.2% and 12.1%), DMAb (6.6% and 9.7%), and TPTD (10.8% and 15.0%) (P
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38 67 < 0.001 between the groups at both 12 and 24 months) in LS and Naïve (5.5% and 8.3%), BP
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40 68 (2.9% and 4.1%), DMAb (0.6% and 2.2%), and TPTD (4.3% and 5.4%) ($P < 0.01$ between
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42 69 the groups at 12 months and $P < 0.001$ at 24 months) in TH, respectively. BMD increase in
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44 70 LS from 12 to 24 months was negatively associated with the levels of bone resorption marker
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46 71 at 24 months. Incidences of major fragility fractures for the respective groups were as
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48 72 follows: Naïve (5.5%), BP (16.2%), DMAb (11.1%), and TPTD (5.9%).

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51 73 *Conclusions:*

1 74 Previous treatment affected the BMD increase of following treatment with ROMO, although
2 75 didn't affect that of following treatment with DMAb after ROMO.
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8 77 **Keywords:** bone mineral density; bone turnover marker; denosumab; prior treatment;
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10 78 postmenopausal osteoporosis; romosozumab
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17 80 **Mini Abstract**
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20 81 In patients with postmenopausal osteoporosis, prior osteoporosis treatment affected the bone
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22 82 mineral density increase of following treatment with 12 months of romosozumab, although
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24 83 **did not** affect that of following treatment with 12 months of denosumab after romosozumab.
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31 85 **1. Introduction**
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34 86 For long-term osteoporosis management, sequential treatment starting with a bone-forming
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36 87 agent followed by an antiresorptive agent has been shown to provide better clinical outcomes
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38 88 and enable the rapid reduction of fracture risk in patients with severe osteoporosis and high
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40 89 risk of fractures [1].
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45 90 Romosozumab (ROMO), a monoclonal anti-sclerostin antibody, is a novel osteoporosis
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47 91 agent, which promotes Wnt signaling by blocking sclerostin [2]. ROMO directly promotes
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49 92 bone formation by osteoblasts and indirectly inhibits bone resorption by osteoclasts by
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51 93 promoting the production of osteoprotegerin (*in vivo* decoy of receptor activator of nuclear
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53 94 factor–kappa B [RANK] ligand [RANKL]) by osteoblasts and osteocytes [3].
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95 Patients who are administered bone-forming agents (such as teriparatide [TPTD] or ROMO)
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2 should be given follow-on therapy with an antiresorptive agent to maintain bone mineral
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4 density (BMD) because of their reversible effects. It has been reported that treatment with
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6 ROMO followed by that with alendronate (ALN) [4] or denosumab (DMAb) [5] further
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8 increased BMD, both of which seemed effective.
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13 On the other hand, the effects of prior treatment on bone anabolic agents have been
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15 investigated. The prior use of DMAb [6] or bisphosphonates (BP) [7] has been shown to
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17 diminish the increase in BMD if follow-on treatment with TPTD is administered. We
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19 previously reported that the prior use of DMAb or BP diminished the increase in BMD if
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21 follow-on treatment with ROMO is administered [8,9]. However, the effects of prior
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23 treatment when ROMO is followed with DMAb are not known. In this study, we aimed to
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25 investigate the effects of prior treatment on treatment response in patients with
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27 postmenopausal osteoporosis treated with ROMO followed by DMAb for 12 months each.
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36 109 **2. Methods** 37

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39 110 *2.1 Study design and patients*
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42 111 This prospective, observational, nonrandomized study was conducted in six centers.
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44 112 Treatment with ROMO was initiated in patients with high fracture risk according to the
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46 definition of the World Health Organization 1998 or the Japanese Guidelines for Prevention
47 113 and Treatment of Osteoporosis 2011 [10]: patients with 1) BMD T-score < -2.5 and ≥ 1
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49 114 fragility fracture, 2) lumbar spine (LS) BMD T-score < -3.3, 3) ≥ 2 vertebral fractures, or 4)
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51 115 semiquantitative (SQ) grade 3 vertebral fracture [11]. Patients with diseases affecting bone
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53 metabolism, such as thyroid or parathyroid diseases, those undergoing hormone replacement
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55 therapy, those with cancer undergoing radiation therapy involving the skeleton, those with
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119 osteomalacia, or those with severely impaired renal function [estimated glomerular filtration
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120 rate (eGFR) < 30 (mL/min/1.73 m²)] were excluded. A total of 154 postmenopausal patients
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121 with osteoporosis who were treatment naïve (Naïve; n = 55) or treated previously with BP (n
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122 = 37), DMAb (n = 45), or TPTD (n = 17) were switched to 12 months of ROMO.
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123 Subsequently, patients were recommended to undergo treatment with DMAb for 12 months
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124 to avoid excessive increase in bone turnover markers and obtain continuous BMD increase
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125 according to a previous report [5] by each attending physician. The detailed patient flow is
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126 presented in the CONSORT flow diagram (Supplementary Fig. 1).
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128 2.2 *BMD assessment*
129 LS (L2–L4), total hip (TH), and femoral neck (FN) BMD were assessed using dual-energy X-
130 ray absorptiometry (Discovery, Hologic, Inc., Waltham, MA, USA) every 6 months after
131 ROMO induction relative to the baseline. BMD data were standardized using the correction
132 method proposed by the Japan Osteoporosis Society in reference to the International Society
133 for Clinical Densitometry Guidance [12]. As previously described, regions of severe
134 sclerosis, vertebral fractures, and surgical sites were excluded from the BMD measurements
135 [13].
136

137 2.3 *Biochemical markers of bone turnover*
138 Bone turnover markers were measured every 6 months relative to the baseline and also 1
139 month after ROMO induction. Isoform 5b of tartrate-resistant acid phosphatase (TRACP-5b;
140 Nittobo Medical Co. Ltd., Tokyo, Japan) was measured as a bone resorption marker, and total
141 N-terminal type I procollagen propeptide (PINP; Roche Diagnostics, Basel, Switzerland) was
142 used as a bone formation marker (a previous report demonstrated that TRACP-5b is a useful
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143 bone resorption marker with higher clinical sensitivity and signal-to-noise ratio compared
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144 with serum cross-linked C-telopeptide of type I collagen [CTX] [14]). Serum 25-
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145 hydroxycholecalciferol [25(OH)D] levels were measured by electrochemiluminescence using
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146 the Elecsys system (Roche Diagnostics, Basel, Switzerland).
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13 148 *2.4 Radiographs*
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17 149 Spinal radiographs were obtained routinely at baseline and every 6 months after ROMO
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19 150 induction. Vertebral fractures of grades ≥ 1 were defined by the SQ method [11]. For patients
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21 151 with symptoms of incidental clinical, vertebral, or nonvertebral fractures, each attending
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23 152 investigator assessed unscheduled radiographs.
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30 154 *2.5 Statistical analysis*
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33 155 The changes in BMD and bone turnover markers were evaluated based on the percentage
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36 156 change from baseline. The differences between study groups were assessed using analysis of
37
38 157 variance (between four groups) for continuous variables and Fisher's exact test (between four
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40 158 groups) for categorical variables. Changes in BMD and bone turnover marker levels from the
41
42 159 baseline to the specified time points within each study group were assessed using Wilcoxon
43
44 160 signed-rank test. Multivariate logistic regression analysis was performed to identify the
45
46 161 factors significantly associated with the BMD increase from 12 to 24 months. The variables
47
48 162 used in the regression analysis were selected by referring to a previous report [15] (age, body
49
50 163 mass index, difference in prior treatment before ROMO, bone turnover markers and BMD at
51
52 164 baseline and 12 months, and change in bone turnover markers from baseline to 24 months
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54 165 and from 12 to 24 months) that possibly influence the effects of BMD increased by DMAb
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56 166 after treatment with bone-forming agent. All statistical analyses were conducted using EZR
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167 software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a
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168 graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria)
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169 [16]. *P* values < 0.05 were considered to indicate statistical significance.
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171 *2.6 Ethical statement*

172 This study was conducted in accordance with the ethical standards of the Declaration of
173 Helsinki and approved by the institutional ethical review board of Osaka University Graduate
174 School of Medicine (approval No. 18258; Osaka University, Graduate School of Medicine)
175 and each of the institutes involved. **Informed consent was obtained from the patients, and opt-**
176 **out information was posted on the hospital's homepage.**

177 **3. Results**

178 Table 1 presents the clinical background of the patients at the time of ROMO induction. No
179 significant differences were observed among the groups in terms of baseline age, body mass
180 index, prior vertebral and nonvertebral fracture incidence ratio, combined vitamin D and
181 calcium ratio, eGFR, and 25(OH)D levels. Significant differences were observed in the
182 duration of prior treatment (*P* < 0.001), interval from final prior treatment prescription (*P* <
183 0.001) (ROMO induction was performed 6.2 [on average] months after last DMAb
184 administration in DMAb group patients), LS BMD (g/cm²; *P* = 0.024), TH BMD (g/cm²; *P* =
185 0.022), FN BMD (g/cm²; *P* = 0.002), T-score (*P* = 0.0047), and serum levels of PINP (*P* <
186 0.001) and TRACP-5b (*P* < 0.001).

187 *3.1 Bone turnover markers*

190 The serum PINP level (Fig. 1a) and its percentage change (Fig. 1b) as well as TRACP-5b
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2 level (Fig. 1c) and its percentage change (Fig. 1d) are shown.
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5 192 In general, PINP level reached its highest value at 1 month after ROMO induction, followed
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7 by a gradual decrease 6 months onwards. The peak response of serum PINP at 1 month was
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9 greatest in the Naïve group, followed by the TPTD group, and the BP group. The transition in
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11 194 the BP group was similar to that observed in the Naïve group, although its absolute value
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13 195 remained in a smaller range. Only the DMAb group maintained its high value until 12
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15 196 months. After DMAb transition, PINP levels of all groups converged to similar levels within
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17 197 the reference range.
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23 199 Regarding TRACP-5b, the Naïve and TPTD groups showed marked decrease 1 month
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25 200 onwards. This tendency was similar in the BP group, although the rate of decrease in this
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27 201 group was lower than that observed in the Naïve and TPTD groups. The DMAb group
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29 202 showed a gradual increase from 1 to 12 months. After DMAb transition, TRACP-5b levels of
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31 203 all groups converged to similar levels within the reference range.
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39 205 *3.2 Changes in BMD*
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42 206 Regarding the change in LS BMD (Fig. 1e), the increase (mean \pm standard error; P value
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44 207 compared with baseline) observed at 12 months was highest in the Naïve group (18.2% \pm
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46 208 1.0%; $P < 0.001$), followed by TPTD (10.8% \pm 1.3%; $P < 0.001$), BP (10.2% \pm 1.1%; $P <$
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48 209 0.001), and DMAb (6.6% \pm 0.7%; $P < 0.001$) groups. BMD at 24 months remained highest in
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51 210 the Naïve group (22.0% \pm 1.1%; $P < 0.001$), followed by TPTD (15.0% \pm 1.2%; $P < 0.001$),
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53 211 BP (12.1% \pm 1.1%; $P < 0.001$), and DMAb (9.7% \pm 1.0%; $P < 0.001$) groups ($P < 0.001$
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55 212 between the groups at both 12 and 24 months). There were no significant differences in the
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57 213 changes in LS BMD from 12 to 24 months between the groups ($P = 0.28$).
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1 214 Regarding the change in TH BMD (Fig. 1f), the increase observed at 12 months was highest
2 215 in the Naïve group ($5.5\% \pm 0.9\%$; $P < 0.001$), followed by TPTD ($4.3\% \pm 1.1\%$; $P = 0.0012$),
3 216 BP ($2.9\% \pm 0.5\%$; $P < 0.001$), and DMAb ($0.6\% \pm 0.9\%$; $P = 0.83$) groups ($P = 0.0015$
4 217 between the groups at 12 months). BMD at 24 months remained highest in the Naïve group
5 218 ($8.3\% \pm 0.9\%$; $P < 0.001$), followed by TPTD ($5.4\% \pm 1.0\%$; $P < 0.001$), BP ($4.1\% \pm 0.6\%$;
6 219 $P < 0.001$), and DMAb ($2.2\% \pm 0.8\%$; $P = 0.024$) groups ($P < 0.001$ between the groups at 24
7 220 months). There were no significant differences in the changes in TH BMD from 12 to 24
8 221 months between the groups ($P = 0.11$).
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20 222 Regarding the change in FN BMD (data not shown), the increase at 12 months was highest in
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22 223 the Naïve group ($5.1\% \pm 1.0\%$; $P < 0.001$), followed by TPTD ($3.4\% \pm 1.1\%$; $P = 0.017$), BP
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24 224 ($3.0\% \pm 0.7\%$; $P = 0.0028$), and DMAb ($0.7\% \pm 0.8\%$; $P = 0.16$) groups ($P = 0.028$ between
25
26 225 the groups at 12 months). BMD at 24 months remained highest in the Naïve group ($7.4\% \pm$
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28 226 1.0% ; $P < 0.001$), followed by TPTD ($5.6\% \pm 1.9\%$; $P = 0.016$), BP ($3.8\% \pm 1.0\%$; $P =$
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30 227 0.0053), and DMAb ($2.9\% \pm 0.9\%$; $P = 0.0071$) groups ($P = 0.054$ between the groups at 24
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32 228 months). There were no significant differences in the changes in FN BMD from 12 to 24
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34 229 months between the groups ($P = 0.36$).
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40 230 Multivariate logistic regression analysis showed that the significant factors indicating LS
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42 231 BMD increase from 12 to 24 months were the absolute level of TRACP-5b at 24 months ($P =$
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44 232 0.029) and the percentage change in TRACP-5b from baseline to 24 months ($P = 0.012$)
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46 233 (Supplementary Table 1). **TH BMD increase from 12 to 24 months was significantly**
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48 234 **associated with the absolute level of TRACP-5b at 12 months ($P = 0.027$) (data not shown).**
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56 236 *3.3 Incidence of fragility fractures*
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1 237 Fifteen patients (n = 15/154; 9.7%) suffered major fragility fractures (including fractures of
2 238 the spine, femur, tibia, patella, humerus, forearm, and rib) during the observation period. In
3 239 the Naïve group, two vertebral fractures and one distal humerus fracture were observed (n =
4 240 3/55; 5.5%). In the BP group, one fracture each was observed for the proximal humerus,
5 241 distal radius, proximal tibia, and patella in addition to two vertebral fractures (n = 6/37;
6 242 16.2%). In the DMAb group, one fracture each was observed for the femoral neck, proximal
7 243 humerus, and rib in addition to multiple vertebral fractures (n = 5/45; 11.1%). In the TPTD
8 244 group, one vertebral fracture was observed (n = 1/17; 5.9%).
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3.4 Incidence of treatment discontinuation

During the observation period, 23 patients (14.9%) discontinued the treatment. Eight patients were lost to follow-up, including change of hospitals. Two patients each discontinued the treatment because of injection pain, dizziness, blood pressure elevation, and death due to unknown reasons. One patient each discontinued the treatment due to subarachnoid hemorrhage attributed to previously indicated aneurysm rupture (Naïve group; 3 weeks after first ROMO administration), cerebral hemorrhage (DMAb group; without history of cerebral or cardiovascular diseases; 7 months after switching from ROMO to DMAb), decreased blood pressure, facial flush, herpes zoster, oral lichen planus, and surgery for valvular disease.

4. Discussion

To the best of our knowledge, this is the first study that demonstrates the effects of prior osteoporosis treatment on response to treatment with ROMO followed by DMAb in patients with postmenopausal osteoporosis.

1 With respect to follow-on treatment after ROMO, a previous study showed that in patients
2 with postmenopausal osteoporosis who were not previously treated for osteoporosis,
3 switching from ROMO to ALN (70 mg orally every week) resulted in a BMD increase of
4 15.2% in LS and 7.1% in TH at 24 months compared with baseline (12 months after ALN
5 transition) [4]. The FRAME extension study demonstrated that switching from ROMO to
6
7 DMAb increased BMD by 16.6% in LS and 8.5% in TH among patients world-wide [5] and
8
9 21.5% in LS and 7.9% in TH among Japanese patients [17] at 24 months compared with
10 baseline (12 months after DMAb transition). Taken together, in Japanese patients, sequential
11 treatment with ROMO and then DMAb may be similar to or even more promising and
12 effective than switching to ALN. Indeed, the Naïve group exhibited a BMD increase of
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14 22.0% in LS and 8.3% in TH at 24 months in the present study, which is comparable to a
15 previous Japanese study [17].

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30 On the other hand, although there were marked differences in bone turnover levels at 12
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32 months between the groups, they all converged to similar levels after the DMAb transition.
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34 We previously reported that in patients who were transitioned from TPTD to DMAb or BP,
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36 the subsequent BMD increase was significantly associated with the rates of decrease of PINP
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38 and TRACP-5b [18]. Indeed, in the present study, the increase in LS BMD from 12 to 24
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40 months due to DMAb was significantly associated with the absolute level of TRACP-5b at 24
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42 months and the percentage change in TRACP-5b from baseline to 24 months. These data
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44 suggest that the BMD increase observed by treatment with an anti-bone-resorptive agent after
45
46 a bone-forming agent treatment may depend on the degree of final bone turnover inhibition.
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49 Consequently, the increased rate of BMD after transition to DMAb was similar between the
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51 groups, although the differences in response to ROMO that we observed between treatment-
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53 naïve and previously treated patients persisted during the subsequent 12 months of DMAb
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55
56 therapy.

1 286 This study has several limitations. The statistical power of the results might be weakened
2 287 because of the small number of patients included. In line with the purpose of the study, this
3 288 was not a randomized study, and there may be some selection bias and differences in the
4 289 baseline patient backgrounds (particularly in BMD and bone turnover marker levels) between
5 290 the groups, which may have affected the results. The contents of prior treatment were not
6 291 uniform within the BP and TPTD groups. We evaluated serum TRACP-5b as a bone
7 292 resorption marker, but serum CTX data were not available. Most patients had vitamin D
8 293 deficiency [serum 25(OH)D < 20 ng/ml] at baseline, which may have affected the results
9 294 even though combined with active vitamin D3. The fracture incidence rates tended to be
10 295 lower in the Naïve (5.5%) and TPTD (5.9%) groups than in the BP (16.2%) and DMAb
11 296 (11.1%) groups, but these results should be confirmed in a larger cohort. However, the
12 297 significance of this study is that it is the first study to demonstrate the effects of prior
13 298 treatment on the response to sequential treatment with ROMO followed by DMAb in a real-
14 299 world setting.

300 In conclusion, the effects of treatment with ROMO for 12 months and follow-on treatment
301 with DMAb for 12 months on BMD increase were significantly affected by prior
302 osteoporosis treatment. However, the corresponding BMD increase after switching from
303 ROMO to DMAb was similar. The insights gained from this study may facilitate the
304 development of a more effective treatment regimen wherein ROMO is followed by DMAb.

305
306 **Statements and Declarations**
307 **Authors' roles**

308 Study design: KE, YE, HT, and MK. Study conduct: KE, YE, MH, and MK. Data collection:
309 KE, HT, YN, MK, AM, YK, GO, and TN. Data analysis: KE and YE. Data interpretation:

310 KE, YE, MK, MH, KT, AG, TM, YF, and TK. Drafting the manuscript: KE and YE.
1
2 311 Supervise: SO and KN. Approving the final version of the manuscript: KE, YE, HT, YN,
3
4 312 MK, AM, YK, MH, GO, TN, KT, AG, TM, YF, TK, SO, and KN. KE takes responsibility for
5
6
7 313 the integrity of the data analysis.
8
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12
13 315 **Conflict of interest**
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15
16 316 KE is affiliated with the Department of Musculoskeletal Regenerative Medicine, Osaka
17
18 317 University, Graduate School of Medicine, which is supported by Taisho. KE and MH have
19
20
21 318 received research grants from Amgen, Asahi-Kasei, Astellas, Chugai, Daiichi Sankyo, Eisai,
22
23
24 319 Eli Lilly, and Ono. KE has received payments for lectures from Amgen, Asahi-Kasei,
25
26 320 Astellas, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, Ono, and Pfizer. HT has received a
27
28
29 321 research grant from Chugai and has received payments for lectures from Asahi-Kasei,
30
31
32 322 Astellas, Chugai, Eisai, Eli Lilly, and Pfizer. YN has received payments for lectures from
33
34 323 Asahi-Kasei, Astellas, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, and Ono. MK has received
35
36 324 payments for lectures from Asahi-Kasei and Astellas. KN has received a research grant from
37
38 325 Astellas and supervises the Department of Musculoskeletal Regenerative Medicine, Osaka
39
40
41 326 University, Graduate School of Medicine, which is supported by Taisho. YE, AM, YK, GO,
42
43 327 TN, KT, AG, TM, YF, TK, and SO declare that they have no conflicts of interest. The
44
45
46 328 funders had no role in the study design, data collection and analysis, decision to publish, or
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48 329 manuscript preparation.
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54 331 **Ethical approval**
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332 All procedures performed in studies involving human participants were in accordance with
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333 the ethical standards of the institutional and/or national research committee and with the 1964
2
334 Helsinki declaration and its later amendments or comparable ethical standards.
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11 336 **Figure legends**
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17 338 **Fig. 1 Serum PINP level (a) and its percentage change (b); serum TRACP-5b level (c)**
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19 339 **and its percentage change (d); percentage change in BMD in the lumbar spine (e) and**
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22 340 **total hip (f)**
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25 341 PINP, N-terminal type I procollagen propeptide; TRACP-5b, isoform 5b of tartrate-resistant
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27 342 acid phosphatase; ROMO, romosozumab; BP, bisphosphonate; DmAb, denosumab; TPTD,
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30 343 teriparatide; BMD, bone mineral density; LS, lumbar spine; TH, total hip.
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33 344 Bars indicate mean \pm standard error. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$; change within
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35 345 each treatment group compared with baseline.
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42 347 **References**
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1 **Table 1. Clinical characteristics of the patients at baseline**

Variable	Naïve group (n = 55)	BP group (n = 37)	DMAb group (n = 45)	TPTD group (n = 17)	P value
Age (years)	73.2 ± 7.8	74.7 ± 7.1	76.1 ± 7.7	75.1 ± 6.7	0.29
Body mass index (kg/m ²)	20.6 ± 2.9	20.5 ± 3.7	20.2 ± 2.7	19.5 ± 2.4	0.60
Prior vertebral fracture (%)	41.8	43.2	53.3	58.8	0.49
Prior nonvertebral fracture (%)	25.5	18.9	15.6	23.5	0.65
ALN (weekly p.o. n = 10/monthly i.v. n = 1)					
Daily TPTD 20µg					
Prior osteoporosis treatment	RIS (weekly and monthly p.o. n = 17)		DMAb 60 mg	(s.c. n = 13)	
	IBN (monthly p.o. n = 2/ monthly i.v. n = 2)		(every 6 months s.c. n = 45)	Weekly TPTD	N.A.
	MIN (monthly p.o. n = 3)			(s.c. n = 4)	
ZOL (yearly i.v. n = 2)					
Duration of prior treatment (months)	0	28.1 ± 23.3	24.1 ± 15.8	12.0 ± 7.9	<0.001
Interval from final prior treatment prescription (months)	0	3.6 ± 5.3	6.2 ± 1.3	1.7 ± 1.0	<0.001
94.5 (52/55) 94.6 (35/37) 100.0 (45/45) 94.2 (16/17)					
Combined VD, % (n/N)	ALF (n = 18)	ALF (n = 13)	ALF (n = 18)	ALF (n = 2)	0.24
	ELD (n = 34)	ELD (n = 22)	ELD (n = 27)	ELD (n = 14)	
Combined ALF, µg/day	0.4 ± 0.2	0.4 ± 0.2	0.5 ± 0.2	0.4 ± 0.2	0.39

Combined ELD, µg/day	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	0.42
Combined Ca, % (n/N)	78.2 (43/55)	62.2 (23/37)	77.8 (35/45)	88.2 (15/17)	0.17
Combined Ca, mg/day	438.1 ± 238.9	617.4 ± 390.4	788.6 ± 561.4	407.3 ± 289.7	<0.001
Lumbar spine BMD (g/cm ²)	0.648 ± 0.128	0.732 ± 0.116	0.702 ± 0.141	0.682 ± 0.123	0.024
Lumbar spine BMD (T-score)	-3.4 ± 1.0	-2.9 ± 0.9	-3.0 ± 1.3	-3.3 ± 1.0	0.087
Total hip BMD (g/cm ²)	0.603 ± 0.079	0.635 ± 0.082	0.573 ± 0.087	0.617 ± 0.094	0.022
Total hip BMD (T-score)	-2.7 ± 0.7	-2.4 ± 0.7	-2.7 ± 0.9	-2.6 ± 0.8	0.12
Femoral neck BMD (g/cm ²)	0.512 ± 0.087	0.572 ± 0.109	0.484 ± 0.087	0.546 ± 0.093	0.002
Femoral neck BMD (T-score)	-3.3 ± 0.7	-2.7 ± 0.8	-3.1 ± 0.8	-2.9 ± 0.8	0.0047
Corrected serum Ca (mg/dl)	9.3 ± 0.4	9.5 ± 0.4	9.5 ± 0.5	9.5 ± 0.3	0.033
eGFR (ml/min/1.73 m ²)	70.9 ± 15.7	71.7 ± 17.9	65.1 ± 20.4	72.5 ± 17.6	0.35
PINP (µg/l)	67.7 ± 31.3	32.2 ± 28.8	30.4 ± 30.9	93.5 ± 72.7	<0.001
TRACP-5b (mU/dl)	505.9 ± 238.2	273.4 ± 133.6	220.3 ± 142.9	437.4 ± 193.8	<0.001
25(OH)D (ng/ml)	14.9 ± 4.6	16.3 ± 5.3	15.4 ± 7.0	14.2 ± 4.7	0.50

2 Mean ± standard deviation. % = number of patients with measurements/total number of patients.

3 Differences between the groups were determined by analysis of variance or Fisher's exact tests.

4 N.A., not applicable; BP, bisphosphonates; DMAb, denosumab; TPTD, teriparatide; p.o., oral administration;

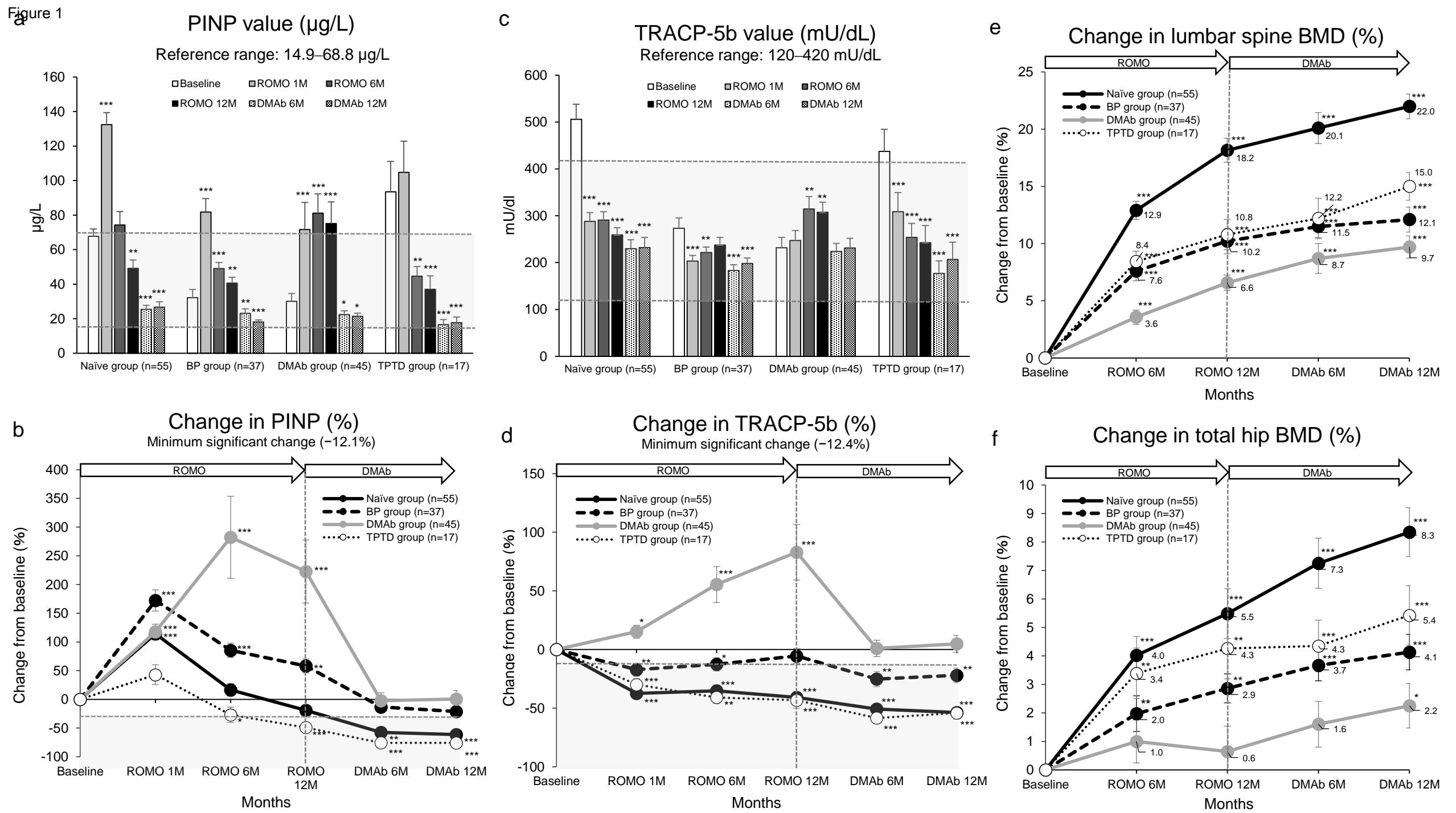
5 i.v., intravenous; s.c., subcutaneous injection; ALN, alendronate; RIS, risedronate; MIN, minodronate; ZOL,

6 zoledronate; VD, vitamin D; ALF, alfacalcidol; ELD, eldecalcitol; Ca, calcium; BMD, bone mineral density;

7 eGFR, estimated glomerular filtration rate; PINP, type I collagen N-terminal propeptide; TRAP-5b, isoform 5b

8 of tartrate-resistant acid phosphatase; 25(OH)D, 25-hydroxycholecalciferol.

Figure 1



Journal: Osteoporosis International

Title: Effects of prior osteoporosis treatment on the treatment response of romosozumab followed by denosumab in patients with postmenopausal osteoporosis

Authors: Kosuke Ebina, MD, PhD*, Yuki Etani, MD, PhD, Hideki Tsuboi, MD, PhD, Yoshio Nagayama, MD, Masafumi Kashii, MD, PhD, Akira Miyama, MD, PhD, Yasuo Kunugiza, MD, PhD, Makoto Hirao, MD, PhD, Gensuke Okamura, MD, PhD, Takaaki Noguchi, MD, PhD, Kenji Takami, MD, Atsushi Goshima, MD, Taihei Miura, MD, Yuji Fukuda, MD, Takuya Kurihara, MD, Seiji Okada, MD, PhD, and Ken Nakata, MD, PhD

***Corresponding author:**

Department of Musculoskeletal Regenerative Medicine and Department of Orthopaedic Surgery, Osaka University, Graduate School of Medicine, 2-2 Yamada-oka, Suita, Osaka 565-0871, Japan
Phone: +81-6-6210-8439; Fax: +81-6-6210-8438

E-mail: k-ebina@ort.med.osaka-u.ac.jp

Supplementary Table 1. Univariate and multivariate logistic regression analysis of the factors associated with the increase in lumbar spine bone mineral density after switching from 12-month romosozumab to 12-month denosumab

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (years)	−0.05 (−0.19, 0.08)	0.44	0.06 (−0.12, 0.25)	0.49
Body mass index (kg/m ²)	0.04 (−0.27, 0.35)	0.78	−0.01 (−0.38, 0.36)	0.98
Prior treatment (Naïve = 1, TPTD = 2, BP = 3, DMAb = 4)	0.36 (−0.38, 1.11)	0.97	0.63 (−0.93, 2.19)	0.42
PINP (at baseline)	0.003 (−0.02, 0.02)	0.73	0.01 (−0.02, 0.05)	0.42
TRACP-5b (at baseline)	−0.004 (−0.008, 0.0003)	0.07	0.01 (−0.004, 0.02)	0.23
PINP (at 12 months)	0.0002 (−0.02, 0.02)	0.98	0.03 (−0.09, 0.15)	0.63
TRACP-5b (at 12 months)	−0.005 (−0.01, 0.001)	0.12	0.01 (−0.02, 0.04)	0.47
PINP (at 24 months)	−0.11 (−0.17, −0.05)	<0.001	−0.07 (−0.35, 0.21)	0.63
TRACP-5b (at 24 months)	−0.01 (−0.02, −0.004)	0.002	−0.03 (−0.06, −0.004)	0.029
Change in PINP from baseline to 24 months (%)	−0.02 (−0.04, −0.007)	0.003	−0.05 (−0.10, 0.0003)	0.051
Change in TRACP-5b from baseline to 24 months (%)	−0.0004 (−0.02, 0.02)	0.97	−0.08 (−0.14, −0.02)	0.012

Change in PINP from 12 to 24 months (%)	-0.03 (-0.05, -0.009)	0.006	0.06 (-0.05, 0.17)	0.30
Change in TRACP-5b from 12 to 24 months (%)	-0.02 (-0.04, -0.002)	0.03	0.007 (-0.07, 0.08)	0.84
Lumbar spine BMD (T-score; at baseline)	0.15 (-0.73, 1.03)	0.74	0.41 (-3.21, 4.04)	0.82
Lumbar spine BMD (T-score; at 12 months)	-0.17 (-1.04, 0.69)	0.69	-0.60 (-4.11, 2.92)	0.73

OR = odds ratio CI = confidence interval.

TPTD, teriparatide; BP, bisphosphonates; DMAb, denosumab; PINP, type I collagen N-terminal propeptide; TRAP-5b, isoform 5b of tartrate-resistant acid phosphatase; BMD, bone mineral density.

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***Corresponding author:**

Department of Musculoskeletal Regenerative Medicine and Department of Orthopaedic Surgery, Osaka University, Graduate School of Medicine, 2-2 Yamada-oka, Suita, Osaka 565-0871, Japan

Phone: +81-6-6210-8439; Fax: +81-6-6210-8438

E-mail: k-ebina@ort.med.osaka-u.ac.jp

