Efficacy and Safety of Bone Management Agents Administered at 12 Weeks vs. 4 Weeks in Patients with Bone Metastases: A Systematic Review

Junya Sato (junya02377@gmail.com)  
International University of Health and Welfare Hospital

Makoto Kodaira  
Kodaira Hospital

Hiroyuki Harada  
Tokyo Medical and Dental University

Haruo Iguchi  
Sasebo Kyosai Hospital

Taichi Yoshida  
Akita University Graduate School of Medicine

Hiroyuki Shibata  
Akita University Graduate School of Medicine

Research Article

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Abstract

**Background:** Bone Modifying Agents (BMAs) have been used to prevent skeletal-related events (SRE) in cancer patients with bone metastases. In this meta-analysis, efficacy and adverse events (AEs) were studied based on a de-escalation strategy in which the BMA dosing interval was prolonged from 4 to 12 weeks.

**Methods:** PubMed, Cochrane, ICHUSHI, and CINAHL were searched for articles on BMA dosing intervals from outcomes measured were the incidence of SRE and related various AEs. A quantitative meta-analysis was performed using a random-effects model to calculate relative risk ratios (RR) and 95% confidence intervals (CI).

**Result:** The meta-analysis included three randomized controlled studies (RCTs) of Zoledronic acid hydrate (ZA) (n = 2,663) and six RCTs (n = 141) on BMA other than zoledronic acid. There was no difference in the incidence of SREs when comparing dosing frequency of 12 versus 4 weeks for BMA (RR = 1.21, 95% CI [0.82-1.78], p = 0.33). Further, AEs related to treatment discontinuation were significantly less frequent with ZA given every 12 weeks than when given every 4 weeks (RR = 0.51 [0.30-0.89], p = 0.02). In particular, renal dysfunction leading to grade ≥3 or discontinuation of treatment with ZA occurred significantly less frequently with every 12-week dosing (RR = 0.33 [0.12-0.91], p = 0.33).

**Conclusion:** The meta-analysis showed no influence of BMA de-escalation on the incidence of SRE, nevertheless, AEs appeared to reduce with the usage of ZA.

Introduction

Approximately 40-70% of the patients with multiple myeloma, breast, prostate, lung, and kidney cancers experience bone metastases[1-5]. Bone metastases can cause bone fractures, decreased level of activities in daily life due to pain and bracing, increased usage of analgesics and their side effects, and the need for radiation therapy. Moreover, the progression of these conditions may lead to life-threatening outcomes such as cardiotoxicity due to hypercalcemia or paralysis due to spinal cord compression. Skeletal-related events (SRE) include radiation therapy related to bone metastases, bone metastasis pain, spinal cord compression, pathological fractures, need for surgery, and hypercalcemia. The 5-year survival rate is 56% in prostate cancer patients without bone metastases in comparison to only 3% in patients with bone metastases[6]. Furthermore, the prognosis for patients with SRE (especially pathological fractures and spinal cord compression) is poorer than those without SRE[7,8]. Therefore, early detection and prevention of SRE development through multimodal treatment (e.g., drug therapy, radiation) are important treatment strategies for patients with bone metastases.

Bone modifying agents (BMAs) such as bisphosphonates (BPs) and anti-receptor activator of nuclear factorκB ligand (RANKL) antibodies are used in the pharmacologic treatment of bone metastases. Zoledronic acid hydrate (ZA) and Pamidronate disodium hydrate (PA) are commonly used BPs. Once the BPs are taken up by osteoclasts apoptosis is induced, thereby suppressing osteoclast function. In
patients with lung cancer and other solid tumors with bone metastases, ZA was found to significantly reduce the incidence of SRE as compared to placebo (39% vs 46%, p = 0.023). Further, it significantly delayed the median time to the first SRE (236 vs. 155 days, p = 0.009)[9]. Furthermore, in breast cancer patients, ZA was more effective than the placebo in reducing the incidence of all SREs, including fractures (25% vs. 40%), bone irradiation (9% vs. 18%), spinal cord compression (4% vs. 12%), hypercalcemia (3% vs. 9%), and bone surgery (0% vs. 1%)1). A systematic review of the effects of BP on cancer patients with bone metastases showed a 30% reduction in the incidence of SRE[10]. Denosumab (Dmab), another BMA used as well as BP, is a monoclonal antibody against RANKL secreted by osteoblasts. RANKL is a ligand-protein that regulates osteoclast function. Inhibition of the pathway by anti-RANKL antibodies inhibits osteoclast activation, thereby reducing bone resorption and progression of cancerous bone lesions. No studies have compared Dmab to placebo with SRE as the outcome. However, Dmab has been compared to ZA for efficacy and safety in breast cancer[11], prostate cancer[12], various solid tumors[13], and multiple myeloma[14]. Studies in breast cancer, prostate cancer, and various solid tumors have reported the superiority of Dmab, and non-inferiority of Dmab versus ZA was reported in the multiple myeloma study. A meta-analysis of these studies found that the risk of SRE when using Dmab is 17% less than that of when using ZA (hazard ratio (HR) = 0.83 [0.76-0.90], p <0.001)[15]. Thus, Dmab is also a useful pharmacotherapy to prevent SRE along with BP. Both of them differ in their method of administration (intravenous vs. subcutaneous), the need for oral calcium supplementation, and their economics. In particular, differences in side effect profiles must be considered for their usage. Common side effects of BMA include fever, bone pain, renal dysfunction, osteonecrosis of the jaw (ONJ), hypocalcemia, and nausea and vomiting. Fever, bone pain, and renal dysfunction are less common with Dmab, and hypocalcemia is less common with ZA[15]. ONJ is reported to be more common in Dmab than in ZA[16]. BMA treatment was discontinued due to side effects in 12-15% and 10-17% of patients treated with ZA and Dmab, respectively[11,12,17]. Therefore, to ensure adequate usage of BMA it is important to reduce its side effects and its usage for a longer duration.

Recently, attempts have been made to prolong the interval between BMA doses. Specifically, a "de-escalation strategy" has been studied in which the standard 4-week (q4w) interval for BPs such as ZA, PA, and Dmab is extended to every 12 weeks (q12w). The de-escalation strategy is expected to maintain efficacy, reduce side effects, and improve health care economics. In previous reports on BMA de-escalation, there were differences in the BMA types used, patient background, and outcomes (SRE, bone metabolism markers, quality of life, pain, etc.), and some results were inconsistent. In this meta-analysis, we studied the efficacy and adverse events (AEs) based on a de-escalation strategy in which the BMA dosing interval was prolonged from 4 to 12 weeks.

**Methods**

Articles, mainly randomized controlled trials (RCTs), were selected by searching PubMed, Cochrane Library, CINAHL, and ICHUSHI. MeSH terms for bone metastases and BMA were used throughout the search scheme and the search date was set to May 2, 2021. Further, a hand search was used to identify
potentially eligible articles, abstracts of scientific meetings, quasi-randomized trials, retrospective observational studies, and articles with health economics considerations. The selected articles included studies on patients with malignancies and bone metastases who used transvenous BP or Dmab for the treatment of bone metastases. Of these articles, studies were selected to facilitate the comparison of standard BMA dosing intervals of q4w with extended dosing intervals of q12w. The endpoints were SRE, symptomatic skeletal event (SSE), and AEs. SRE was defined as pathologic fracture, radiation therapy to the bone, spinal cord compression, surgery involving bone, and hypocalcemia. SSE was defined as symptomatic pathological fracture, radiation therapy to the bone, spinal cord compression, surgery involving bone, and hypercalcemia. Literature searches, article selection, and bias risk assessments were conducted independently, and their quality was verified by two or more co-researchers. The risk of bias in recruitment studies was assessed according to the Medical Information Distribution Service (Minds) guidelines[18]. Bias risk endpoints included 1) randomization, 2) concealment of allocation, 3) blinding of treatment providers or participants, 4) blinding of outcome assessment, 5) selective bias reporting, 6) case attrition bias, and 7) other biases that may affect the validity of the study. Each bias risk was rated on a scale of low, moderate, or high. Statistical analysis was performed using RevMan 5.3 software (Nordic Cochran Centre, Copenhagen, Denmark, 2014). A random-effects model was used for the analysis and was used to calculate risk ratios (RR) and their 95% confidence intervals (CI). The I² approach was used to measure heterogeneity between studies, with >50% considered a high level, 25%-50% a medium level, and <25% a low level of heterogeneity.

Results

Selecting a study

The process of extracting articles is shown in Figure 1. A total of 103 articles were extracted from each search engine (51, 26, 13, and 13 articles were extracted from PubMed, Cochrane Library, CINAHL, and ICHUSHI, respectively). After primary screening by title and abstract, 26 articles were selected. These 26 articles were then screened for full text, and a total of 18 articles were excluded: 14 articles were duplicates or did not include SREs or AEs in the outcomes, three were meta-analyses and one was a guideline document. Only one article was included by hand search. Finally, a total of nine articles were used in the meta-analysis.

Research characteristics

A total of 3,678 patients were evaluated in nine RCTs. The characteristics of the study are shown in Table 1. The median number of patients in each study was 255 (minimum 30, maximum 1,822). There were relatively few studies with small patient populations. The extracted articles used different BMA treatments, three of them studied only ZA (CALGB-70604[19], OPTIMIZE-2[20], and ZOOM[21]), one only PA (REFORM[22]), one only Dmab (REDUCE[23]), and four studied Dmab in addition to ZA and PA (REaCT[24], Fizazi K[25], Lipton A (2007)[26], and Lipton A (2008)[27]). Of the nine RCTs, four were non-inferiority trials. The diseases included in the studies were breast cancer, prostate cancer, and multiple
myeloma. Regarding the BMA use in the study subjects before randomization, four studies included only patients who reported previous use of BMA (OPTIMIZE-2[20], ZOOM[21], REFORM[22], and REDUCE[23]) and three studies included a few patients with previous use of BMA (CALGB-70604[19], REaCT[24], and Fizazi K[25]), and two studies included only BMA-naive patients (Lipton A (2007)[26] and Lipton A (2008) [27]). Three studies had SRE as the primary endpoint (CALGB-70604[19], OPTIMIZE-2[20], and ZOOM[21]); one study that evaluated the quality of life (REaCT[24] and REDUCE[23]) had SSE as the primary endpoint, but at the time of investigation, hypocalcemia was reported. The remaining four studies evaluated bone metabolism markers. The duration of treatment was mostly 1-2 years for studies with SRE as the primary endpoint, and 13-25 weeks for studies with bone metabolism markers as the endpoint. In REDUCE[23], which is currently validating denosumab de-escalation, the interim analysis results were reported at 3.5 years.

Bias risk

Other than OPTIMIZE-2[20], most of the studies were open-label studies in which a placebo was not administered at weeks 4 and 8 in the q12w group. The risk of performance bias and detection bias was an issue in these studies. Other biases include those observed in Lipton's study[26,27] in which all BP was assigned to the q4w group and differing clinical doses from 30 mg to 180 mg Dmab was administered to the q4w and q12w groups. There was no fatal risk of bias in the other assessment items. The risk of bias for each trial and the integrated risk distribution are shown in Supplemental Figure 1.

Integration results for each assessment item

SRE

The results of the SRE integration are shown in Figure 2. When integrating SRE from three studies that included only ZA, we found for q12w and every q4w SRE incidence was 331/1,323 (25.0%) and 7/1,327 (25.4%), respectively, with no difference in dosing schedule RR = 0.98 [0.86-1.12], p = 0.79. Similarly, three other studies that included BMA other than ZA were integrated (Figure 2), and we found no difference in SRE incidence (52/182 (28.6%) vs. 21/181 (11.6%), RR = 1.51 [0.46-4.97], p = 0.50). In the integrated analysis of the six studies that included all BMAs, SRE was 383/1,505 (25.4%) and 358/1,508 (23.7%) for q12w and q4w, respectively, with no difference by dosing schedule (RR = 1.21 [0.82-1.78], p = 0.33). However, heterogeneity between studies was high (75%).

AEs

The results of the integration of AEs are shown in Figure 3. There was no influence of dosing schedule on any grade level of AEs in either the integration of the two studies that included ZA or in the integration that included two non-ZA studies. In the integration of the four studies, 506/581 (87.1%) and 569/626 (90.9%) AEs were observed for q12w and q4w, respectively, with no difference (RR = 0.97, [0.92-1.02], p = 0.23). Heterogeneity among studies was moderate (48%) (Figure 3A).
In the integration of the three ZA-only studies, when AEs were limited to grade $\geq 3$, the incidence of AEs was 38/1,322 (2.9%) and 74/1,325 (5.6%) for q12w and q4w, respectively. AEs were significantly less frequent for q12w than for q4w (RR = 0.51, [0.30-0.89], $p = 0.02$). In the integration of the two studies with BMAs other than ZA, there was no difference in incidence between q12w and q4w dosing schedules (35/215 [16.3%] vs 23/176 [13.1%], RR = 1.47, [0.38-2.36] $p = 0.34$). Similarly, the integration of all five studies showed no difference (73/1537 [4.7%] vs. 97/1501 [6.4%], RR = 0.73, [0.38-1.40], $p = 0.34$).

Renal dysfunction

The results of the integration of renal dysfunction studies are shown in Figure 4. In the integration of the three ZA-only studies, the incidence for all grades of renal dysfunction was 154/1293 (11.9%) and 195/1289 (15.1%) for q12w and q4w, respectively, with a significantly lower risk of a renal dysfunction for q12w than q4w (RR = 0.75, [0.59-0.94], $p = 0.01$). Only one non-ZA study showed no difference. In the integration of all four studies, the incidence of renal dysfunction in q12w and q4w was 158/1,423 (11.1%) and 199/1,422 (14.0%), respectively, with a significantly lower risk of renal dysfunction for q12w than q4w (RR = 0.75 [0.60-0.94], $p = 0.01$). There was no heterogeneity among all studies (0%) (Figure 4A). When renal dysfunction was limited to grade $\geq 3$ or treatment discontinuation, the two ZA studies were integrated (none of the studies included non-ZA). The results showed a reduced incidence of renal dysfunction in q12w compared to q4w (5/1039 (0.5%) vs 16/1050 (1.5%), RR = 0.33 [0.12-0.91], $p = 0.03$). There was no heterogeneity between studies (0%) (Figure 4B).

ONJ and hypocalcemia

ONJ and hypocalcemia results are shown in Figure 5. The incidence of ONJ did not differ in q12w and q4w in either integrated three ZA-only studies or the one non-ZA study. Integration of these four studies showed no difference (14/1452 (1.0%) vs. 24/1458 (1.6%), RR = 0.61, [0.31-1.18], $p = 0.14$). There was no heterogeneity between studies (0%) (Figure 5A).

Similarly, the incidence of hypocalcemia did not differ between q12w and q4w in ZA-only study nor the two studies including BMA other than ZA. Integration of these three studies showed no difference (316/1,025 (30.8%) vs. 355/1,056 (33.6%), RR = 0.92, [0.81-1.04], $p = 0.17$). There was no heterogeneity between studies (0%) (Figure 5B).

Other AEs

Results for bone pain, nausea, and vomiting are shown in Figure 6. The results reported for all three of these AEs is from the integration of two ZA-only studies. There was no difference in incidence of bone pain between q12w and q4w (104/411 (25.3%) vs 114/414 (27.5%), RR = 0.92[0.73-1.16], $p = 0.47$) (Figure 6A). The incidence of nausea also did not differ between q12w and q4w (77/411 (18.7%) vs 92/414 (22.2%), RR = 0.84 [0.65-1.10], $p = 0.20$) (Figure 6B). Furthermore, there was no difference in incidence between q12w and q4w in vomiting (48/411 (11.7%) vs. 55/414 (13.3%), RR = 0.85 [0.53-1.39],
Heterogeneity between the two studies was none (0%) for outcome of bone pain and nausea, and moderate (39%) for vomiting.

**Discussion**

The current study integrated and analyzed nine studies, including three pivotal studies using ZA alone, and six included other BMAs such as Dmab and PA. The influence of dosing schedule extension (de-escalation) on the efficacy of ZA as measured by SRE was non-inferior in all three pivotal studies, and the results were supported in the current integrated analysis. Furthermore, there was no influence of the extended dosing schedule on SRE in the three studies that included BMAs other than ZA, nor in the integration of all six studies that included any type of BMA. Although there is heterogeneity in the results of integrations of non-ZA studies, de-escalation of the BMA might be less likely to lead to a reduction in effectiveness. The current study was an integrated analysis focusing on the benefits of de-escalation: all AEs such as renal dysfunction, ONJ, hypocalcemia, bone pain, and gastrointestinal toxicity, were reduced with the de-escalation strategy. In particular, there was almost a 40% reduction in renal dysfunction in ZA with prolonged dosing schedules, and consequently, there was a reduction in treatment discontinuation.

ONJ and atypical femur fractures (AFF) are problems with the long-term use of BP[28] which is dependent on the cumulative dose of BP and the duration of treatment[29–31]. Therefore, de-escalation of BMA was expected to reduce the incidence of ONJ. However, in this integration analysis, there was no influence of de-escalation of the BMA on the incidence of ONJ. Since the time to ONJ onset is longer than 3–4 years[32], the short observation period of the integrated study may have affected the influence of de-escalation. No influence of BMA de-escalation has also been observed on the incidence of hypocalcemia. This may be due to the influence of routine prophylactic vitamin D and Ca supplementation in each study that included any type of BMA. In a report comparing the cost-effectiveness of q4w ZA, q12w ZA, and q4w Dmab in breast cancer patients, the QALYs were the same for all treatments. The cost of q12w ZA was shown to be 90% and 40% less costly than q4w Dmab and q4w ZA, respectively[33]. These results suggest that de-escalation of BMA, especially ZA, is an important therapeutic strategy due to its superiority in medical economics and ability to avoid treatment discontinuation by reducing renal dysfunction.

Three meta-analyses have assessed BMA dosing schedules similar to this study[34–36]. The list is presented in Supplemental Table 1. Awan et al. integrated two studies (OPTIMIZE-2[20] and ZOOM[21]) to compare renal dysfunction (increased serum creatinine) in q4w and q12w. The results showed that the incidence was 5/430 (1.2%) and 12/433 (2.8%), respectively, with no significant difference (RR = 0.41 [0.15–1.16], p = 0.09)[34]. In this study, ZA was administered in a total of 2,582 cases in three studies and a reduction in overall grade renal dysfunction was observed that led to treatment discontinuation. This difference in results might have been influenced by sample size. The novelty of this study is that it demonstrates a reduction in renal dysfunction with a prolonged ZA dosing schedule.
The American Society of Clinical Oncology, in collaboration with Cancer Care Ontario, revised its guidelines in 2017. For breast cancer patients receiving ZA, the Society strongly recommends dosing for 12 weeks in addition to every 3–4 weeks because the benefits outweigh the harms[37]. However, the following limitations should be considered for administering BMA every 12 weeks in all patients. First, several studies that evaluated bone metabolic markers showed significant variations in bone metabolic markers[19–22]. Although many have concluded that changes in these bone metabolic markers do not reflect clinical symptoms such as SRE; nevertheless, whether or not the de-escalation strategy should be changed due to increased bone metabolic markers needs to be further studied. Second, 37% of the patients in the integrated study had received some prior BMA. De-escalation may be useful as a "maintenance therapy" in patients whose bone metastases were controlled with BMA usage prior to randomization. However, according to a meta-analysis by Awan et al., the extended dosing schedule had no influence in either BMA native or previously treated patients[34]. Whether the de-escalation strategy can be applied to BMA native patients, i.e., whether 12-week dosing of BMA can replace 4-week dosing as standard therapy, needs further investigation. Third, most studies have a maximum observation period of only two years; hence, it is questionable whether the efficacy of de-escalation is maintained over a longer period. A Swedish study that followed the prognosis of metastatic breast cancer patients from 1985 to 2016 showed a dramatic increase in median survival from 13 to 33 months[38]. Although BMA is likely to be used by patients with bone metastases until the end of life, there is uncertainty as to whether the benefits of de-escalation strategies will be maintained during this long period. Fourth, patients in the integrated article were limited to breast cancer, prostate cancer, and multiple myeloma. In the CALGB-70604[19] study, cancer type had no influence on the incidence of SRE under the de-escalation strategy, but it is important to note that renal and lung cancers with a high incidence of bone metastases were not included in that study. Fifth, no high-quality RCTs have assessed the usage of BMAs other than ZA. In the REnACT[24] study, PA and Dmab were evaluated mixed as well as ZA as BMA. The REFORM[22] study, which evaluated only PA, had insufficient information on AEs. In the reports by Lipton et al[26,27], ZA and PA were mixed in the BP group, and the BP and Dmab dosing schedules were not equally randomized. In the REnACT[24] study, which examined de-escalation using various BMAs, the subset analysis showed no difference in SRE incidence between BMAs, but there may be differences in the drug profiles of BP and Dmab. After administration, Dmab circulates in the body and inhibits RANKL expressed on lymphocytes, it has a half-life of one month. However, BP is incorporated into bone resorption sites and has a long half-life of several years in bone[39]. Uncertainty might remain as to whether de-escalation of Dmab and BP is equivalent when they are pharmacologically and pharmacokinetically different.

AFFs are a problem with the long-term administration of BP. These are due to the transformation of osteolytic metastases into osteosclerotic lesions that is dependent on the BP dosage and the length of treatment[40]. Reducing BP dosage may decrease AFF. Moreover, there is concern that Dmab for osteoporosis may cause a "rebound," a rapid increase in bone metabolism after discontinuation of treatment, resulting in an increase in vertebral fractures[41]. Although reproducibility in cancer patients with bone metastases has not been reported, strategies may be needed to facilitate the continuation of
Dmab usage while reducing side effects. Therefore, De-escalation of BMA with Dmab would be a useful option. Results of longer-term, larger RCTs that include Dmab are expected in the future.

**Conclusion**

Prolonging the dosing interval of ZA among BMAs from the standard 4-week interval to a maximum of 12 weeks might have benefits in reducing the risk of renal dysfunction without increasing SRE.

**Declarations**

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Not applicable.

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**Competing Interests**

The authors have no relevant financial or non-financial interests to disclose.

**Availability of data and material**

All data generated or analyzed during this study are included in this published article.

**Code availability**

Not applicable.

**Author Contributions**

Junya Sato and Makoto Kodaira contributed to the conception and design of the study. Junya Sato conducted the data collection and initial analysis. The first draft of the manuscript was written by Junya Sato and read by Hiroyuki Shibata, which was revised and agreed by member of diagnosis and treatment of bone metastasis: comprehensive guideline (the 2nd Edition) developing group.

**Ethics approval**

Not applicable.

**Consent to participate**

Not applicable.
Consent to publish

Not applicable.

References


Tables

Table 1 is available in the Supplementary Files section.

Figures
Figure 1. Selection process for articles

Figure 1

See image above for figure legend.

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<th>Study or Subgroup</th>
<th>q12w Events</th>
<th>Total Events</th>
<th>q4w Events</th>
<th>Total Events</th>
<th>Risk Ratio M-H, Random, 95% CI Year</th>
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Figure 2. Forest plot of studies including ZA only or BMA other than ZA comparing q12w vs q4w for SRE.
**Figure 2**

See image above for figure legend.

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<th>Study or Subgroup</th>
<th>q12w Events</th>
<th>q12w Total</th>
<th>q4w Events</th>
<th>q4w Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Only ZA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZOOM(2013)</td>
<td>159</td>
<td>208</td>
<td>184</td>
<td>216</td>
<td>18.9%</td>
<td>0.89 [0.81, 0.98] 2013</td>
</tr>
<tr>
<td>OPTIMIZE-2(2017)</td>
<td>189</td>
<td>202</td>
<td>189</td>
<td>198</td>
<td>36.2%</td>
<td>0.98 [0.93, 1.03] 2017</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>411</td>
<td>414</td>
<td>55.1%</td>
<td></td>
<td></td>
<td>0.94 [0.84, 1.05]</td>
</tr>
<tr>
<td>Total events</td>
<td>348</td>
<td>373</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.00; Chi^2 = 4.40, df = 1 (P = 0.04); I^2 = 77%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.05 (P = 0.26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**BMA other than ZA**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>q12w Events</th>
<th>q12w Total</th>
<th>q4w Events</th>
<th>q4w Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipton(2007)</td>
<td>76</td>
<td>85</td>
<td>155</td>
<td>169</td>
<td>21.1%</td>
<td>0.97 [0.89, 1.06] 2007</td>
</tr>
<tr>
<td>Lipton(2008)</td>
<td>82</td>
<td>85</td>
<td>41</td>
<td>43</td>
<td>23.8%</td>
<td>1.01 [0.94, 1.09] 2008</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>170</td>
<td>212</td>
<td>44.9%</td>
<td></td>
<td></td>
<td>1.00 [0.94, 1.05]</td>
</tr>
<tr>
<td>Total events</td>
<td>506</td>
<td>569</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.00; Chi^2 = 6.80, df = 3 (P = 0.12); I^2 = 48%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.20 (P = 0.23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi^2 = 0.77, df = 1 (P = 0.38), I^2 = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 3**

Forest plot of studies including ZA only or BMA other than ZA comparing 4-weeks vs 12-weeks dosing schedule for A) AEs(any grade), B) AE leading to treatment discontinuation.

**Figure 3**

See image above for figure legend.
### A)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>q12w Events</th>
<th>q12w Total</th>
<th>q4w Events</th>
<th>q4w Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZOOM(2013)</td>
<td>1</td>
<td>209</td>
<td>2</td>
<td>216</td>
<td>0.9%</td>
<td>0.51 [0.05, 5.72] 2013</td>
</tr>
<tr>
<td>CALGB-70604(2017)</td>
<td>137</td>
<td>882</td>
<td>174</td>
<td>875</td>
<td>85.7%</td>
<td>0.74 [0.58, 0.95] 2017</td>
</tr>
<tr>
<td>OPTIMIZE-2(2017)</td>
<td>16</td>
<td>202</td>
<td>19</td>
<td>198</td>
<td>10.8%</td>
<td>0.81 [0.40, 1.63] 2017</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1293</td>
<td>1289</td>
<td>97.4%</td>
<td>195</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>154</td>
<td></td>
<td>195</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 2 (P = 0.93); I² = 0%
Test for overall effect: Z = 2.49 (P = 0.01)

### B)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>q12w Events</th>
<th>q12w Total</th>
<th>q4w Events</th>
<th>q4w Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZOOM(2013)</td>
<td>1</td>
<td>209</td>
<td>2</td>
<td>216</td>
<td>0.9%</td>
<td></td>
</tr>
<tr>
<td>CALGB-70604(2017)</td>
<td>137</td>
<td>882</td>
<td>174</td>
<td>875</td>
<td>85.7%</td>
<td>0.41 [0.13, 1.29] 2017</td>
</tr>
<tr>
<td>OPTIMIZE-2(2017)</td>
<td>16</td>
<td>202</td>
<td>19</td>
<td>198</td>
<td>10.8%</td>
<td>0.16 [0.02, 1.34] 2017</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1293</td>
<td>1289</td>
<td>97.4%</td>
<td>195</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>154</td>
<td></td>
<td>195</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 3 (P = 0.95); I² = 0%
Test for overall effect: Z = 2.45 (P = 0.01)
Test for subgroup differences: Chi² = 0.19, df = 1 (P = 0.66), I² = 0%

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**Figure 4**

Forest plot of studies including ZA only or BMA other than ZA comparing 4-weeks vs 12-weeks dosing schedule for A) renal dysfunction (any grade), B) renal dysfunction (grade ≥ 3 or treatment discontinuation).

### Figure 4

See image above for figure legend.
Figure 5. Forest plot of studies including ZA only or BMA other than ZA comparing 4-weeks vs 12-weeks dosing schedule for A) Osteonecrosis of the jaw, B) Hypocalcemia.

### Figure 5

See image above for figure legend.
Figure 6. Forest plot of studies including ZA comparing 4-weeks vs 12-weeks dosing schedule for A) bone pain, B) nausea, C) vomiting.

Figure 6

See image above for figure legend.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.tif
- Table1continued.tif
- SupplementalTable1.tif
- SupplementalFigure1.tif