Safety of Denosumab Versus Zoledronic Acid in Patients with Bone-related Diseases
A Systematic Review and Meta-analysis

**Abstract**

Introduction
Both Dmb and ZA have been widely used in the prevention and treatment of bone-related diseases, while which drug is an optimal treatment in terms of safety and efficacy remains controversial.

Material and methods
PubMed, Embase, Web of Science, the Cochrane Central Library, and ClinicalTrials.gov were systematically searched up to 1st January 2021, and were evaluated by Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. Randomized controlled trials comparing Dmb versus ZA in patients with bone-related diseases were included.

Results
A total of 13 studies involving 21042 participants were included. The incidence of total adverse events was significantly lower in patients receiving Dmb treatment than in those undergoing ZA treatment (OR = 0.84, 95% CI = 0.75–0.94, P = 0.003). 9 trials comparing Dmb with ZA further showed that Dmb was significantly better than ZA in controlling serious adverse events (OR = 0.91, 95% CI = 0.85–0.99, P = 0.02). Compared to ZA, Dmb was correlated with a lower incidence of skeletal-related events (OR = 0.77, 95% CI = 0.70–0.85, P = 0.00001). However, no significant difference was found in the rate of infection events between Dmb and ZA (OR = 1.06, 95% CI = 0.93–1.20, P =0.39).

Conclusions
This study demonstrated superiority of Dmb over ZA in treating bone-related diseases in terms of safety and efficacy.
Safety of Denosumab Versus Zoledronic Acid in Patients with Bone-related Diseases

A Systematic Review and Meta-analysis

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Abstract

Objective: To compare the safety of denosumab (Dmab) versus zoledronic acid (ZA) in patients with bone-related diseases.

Background: Both Denosumab and zoledronic acid have been widely used in the treatment of bone-related diseases, while which drug is an optimal treatment in terms of safety remains controversial.

Methods: PubMed, Embase, Web of Science, the Cochrane Central Library, and ClinicalTrials.gov were systematically searched up to 1st January 2021, and were evaluated by Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. Randomized controlled trials comparing relevant outcomes of Dmab versus ZA in patients with bone-related diseases were included.

Results: A total of 13 studies involving 21042 participants were included. The incidence of total adverse events was significantly lower in patients receiving Dmab treatment than in those undergoing ZA treatment (OR = 0.84, 95% CI = 0.75–0.94, P = 0.003). Nine trials comparing Dmab with ZA further indicated that Dmab was significantly better than ZA in controlling the incidence of serious adverse events (OR = 0.91, 95% CI = 0.85–0.99, P = 0.02). Compared to ZA, Dmab administration was correlated with a lower risk of skeletal-related events (OR = 0.77, 95% CI = 0.70–0.85, P = 0.00001). However, no significant difference was found
in the rate of infection events between Dmab and ZA (OR = 1.06, 95% CI = 0.93–1.20, P = 0.39).

**Conclusion:** This study demonstrated superiority of Dmab over ZA in treating bone-related diseases in terms of safety.

**Keywords:** Denosumab, Zoledronic acid, Bone-related diseases, Adverse events.

**Introduction**

With the increase of tumor incidence and the aging of the population, the prevalence of bone-related diseases along with the demand for corresponding medications is growing. We attached great importance to bone-related diseases\(^1\)-\(^3\). As two potent antiresorptive agents, both denosumab (Dmab) and zoledronic acid (ZA)\(^4\) have been widely used in the treatment of bone-related diseases, including but not limited to osteoporosis\(^5\),\(^6\), bone metastases secondary to solid tumors\(^7\)-\(^9\), multiple myeloma\(^10\),\(^11\) and giant cell tumor of bone\(^12\),\(^13\). As a potent intravenous bisphosphonate, ZA plays a critical role in the prevention of skeletal complications in bone-related diseases\(^5\),\(^14\). Dmab is a fully human monoclonal antibody of the immunoglobulin G2 isotype, which functions against the receptor activator of nuclear factor κB ligand (RANKL) and thereby inhibits osteoclast activation and function\(^15\), and its use is significantly less limited to renal toxicity\(^16\). Growing evidence suggests that Dmab is superior in terms of efficacy\(^17\),\(^18\), safety\(^5\) and even cost-
effectiveness\textsuperscript{19,20} over ZA. Published meta-analyses comparing the efficacy between Dmab and ZA for treatment of bone metastases in patients with solid tumors demonstrated that Dmab was better than ZA in preventing complications and delaying the onset of skeletal-related events (SREs)\textsuperscript{21-23}. However, meta-analysis evaluating the safety between Dmab and ZA is still insufficient. In the few studies evaluating this, the use of both drugs was confined to the treatment of patients with bone metastases\textsuperscript{16,21,23}. With the continuous expansion of indications of both drugs and increased interest in identifying the optimal treatment for bone-related diseases, there is necessity to comprehensively compare the safety of Dmab and ZA based on a wide range of bone-related diseases, which is also an important aspect to guide the clinical medication. Therefore, in this study, we conducted a systematic review and meta-analysis based on clinical trials to compare the safety and efficacy between Dmab and ZA in patients with bone-related diseases.

\textbf{Materials and Methods}

Registration of this systematic review has been completed on the PROSPERO (International Prospective Register of Systematic Reviews) website, under the registration number CRD42021227328. This systematic review was conducted with adherence to the guidelines of Preferred
Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement\textsuperscript{24}.

**Study Selections**

Relevant studies were searched and identified by individually searching the following databases: PubMed, Embase, Web of Science, the Cochrane Central Library, and ClinicalTrials.gov up to 1st January 2021. For all databases, the following key terms were used for searching: “Denosumab”, “zoledronic acid” and “bone”. The study design was limited to randomized controlled trials (RCTs). This meta-analysis adhered to the Critical Appraisal Skills Programme (CASP) Checklist. Eligibility assessment was performed by two independent reviewers (L.W.H. and J.R.Y.). Disagreements between reviewers were resolved by group discussion and consensus.

**Inclusion and Exclusion Criteria**

Eligibility was assessed by two independent reviewers (L.W.H. and J.R.Y.), with consensus reached by discussing conflicts with a third investigator (L.Y.). Assessments were performed and repeated twice. Only RCTs were included. First, the titles and abstracts were assessed. Full texts of potentially qualified studies were then obtained and carefully reviewed. Reviewers were not blinded to the authorship of the studies. Dissertations, conference proceedings, and studies in non-English languages were excluded.
Outcomes of Interest

The primary outcome measure was the rate of adverse events. The secondary outcome measures were the rate of serious adverse events, SREs and infection events.

Data Collection

The following data were extracted: first author, year of study, country of origin, study population, number of patients, basic demographic characteristics, treatment information and data of outcomes of interest. The data were extracted and cross-checked independently by two authors (L.W.H. and J.R.Y.). Disagreements were resolved through deep discussion with a third reviewer (L.Y.) until we have reached a consensus.

Evaluation of Quality of Evidence

The methodological quality of the selected studies was blindly evaluated by two independent reviewers (L.W.H. and J.R.Y.). Disagreements were discussed among the group and resolved by a third assessor (L.Y.). The study quality was assessed using the CASP Checklist (Supplementary Table 1), which evaluates the risk of bias and comprises 11 items related to methodological quality and statistical reporting. Discrepancies and disagreements were resolved by consensus.

Statistical Analysis

Data analyses were performed using the Cochrane Collaboration’s Review Manager program (RevMan version 5.3; Cochrane Collaboration,
Oxford, UK). Meta-analysis was conducted to calculate pooled odds ratios (ORs) with 95% confidence intervals (CIs). We evaluated heterogeneity across studies using the Cochrane chi-square ($\chi^2$) and quantified with the $I^2$ statistics$^{25}$. $I^2$ values of 25%, 50% and 75% represented low, moderate and high heterogeneity, respectively$^{26}$. Fixed-effects or random-effects models were used accordingly. The publication bias was detected by funnel plots and was statistically examined by Egger’s test$^{27}$. The Egger’s test was performed in STATA version 16 (StataCorp, College Station, TX).

Results

Literature Search

A flow diagram of the literature search was shown in Figure 1. Among 565 potentially eligible articles, 13 fulfilled the inclusion criteria. Initially, through the electronic database search, we identified 565 citations. Examinations of the reference lists in all relevant papers, recent editorials, and related review articles yielded no further studies for evaluation. Non-RCTs were excluded and the remaining 26 articles were then selected after reading the titles and abstracts. After reading the full texts, 13 studies were further excluded because they did not report relevant outcomes. The remaining 13 RCTs met our inclusion criteria and were ultimately included in the qualitative analysis and final meta-analysis.
Study Characteristics

The characteristics of enrolled RCTs were presented in Table 1. Our meta-analysis included 21042 patients (10073 men and 10969 women) who were diagnosed with bone-related disease from six different countries. Among them, 10535 (50.1%) patients were treated with Dmab and 10507 (49.9%) patients were treated with ZA. The results of the quality assessment of the included RCTs were detailed in Table 2.

Primary Outcome

Adverse events

Ten of the included studies reported the overall rate of adverse events. The adverse events rate was 86.3% (6581/7623) in the Dmab group and
87.6% (6644/7584) in the ZA group. (odds ratio [OR] = 0.84, 95% CI = 0.75–0.94, P = 0.003) (Figure 2).

Secondary Outcomes

Serious adverse events

Nine RCTs reported relevant data regarding the rate of serious adverse events. The incidence of serious adverse events was significantly lower in the Dmab group compared with the ZA group (OR = 0.91, 95% CI = 0.85–0.99, P = 0.02) (Figure 3).
Skeletal-related Events (SREs)

The SREs rates were reported in four RCTs. The overall SREs rate was 40.5% (37.5% in the Dmab group and 43.5% in the ZA group). Dmab contributed to a lower incidence of SREs. (OR = 0.77, 95% CI = 0.70–0.85, P = 0.00001) (Figure 4).

| Study or Subgroup | Denosumab Events | Denosumab Total | Zoledronic Events | Zoledronic Total | Weight | Odds Ratio M H Fixed, 95% CI |
|-------------------|------------------|----------------|------------------|------------------|--------|--------------------------|
| Martin 2011       | 341              | 368            | 651              | 37.5%            | 0.62   | [0.56, 0.68]             |
| Miguel 2012       | 318              | 332            | 690              | 26.3%            | 0.60   | [0.55, 0.65]             |
| Salahi 2015       | 494              | 604            | 651              | 37.5%            | 0.60   | [0.57, 0.62]             |
| Yadavhan 2012     | 276              | 333            | 690              | 23.2%            | 0.60   | [0.56, 0.66]             |
| **Total (95% CI)**| **3812**         | **3812**       | **100%**         | **0.77 [0.70, 0.85]** |
| Total events      | 1341             | 1680           |                  |                  |        |                          |

Figure 4 Forest plot for the incidence of SREs in denosumab compared with zoledronic acid

Infection events

Four studies involving 6594 patients were pooled and analyzed. These four trials comparing Dmab with ZA in patients with bone-related disease showed no significant difference between two drugs in the incidence of infection events (OR = 1.06, 95% CI = 0.93–1.20, P =0.39) (Figure 5).

| Study or Subgroup | Denosumab Events | Denosumab Total | Zoledronic Events | Zoledronic Total | Weight | Odds Ratio M H Random, 95% CI |
|-------------------|------------------|----------------|------------------|------------------|--------|-----------------------------|
| Alimohamadian 2019| 473              | 494            | 1013             | 32.6%            | 0.91   | [0.89, 1.08]               |
| Alimohamadian 2016| 193              | 168            | 452              | 18.4%            | 1.29   | [1.19, 1.38]               |
| Doi 2011          | 128              | 119            | 276              | 17.6%            | 1.13   | [1.04, 1.26]               |
| Kamin 2011        | 402              | 375            | 1046             | 30.6%            | 1.35   | [1.24, 1.46]               |
| **Total (95% CI)**| **3396**         | **3288**       | **100%**         | **1.06 [0.93, 1.20]** |
| Total events      | 1196             | 1165           |                  |                  |        |                             |

Figure 5 Forest plot for the incidence of infection events in denosumab compared with zoledronic acid
Publication Bias

-Funnel plots for the incidence of adverse events, serious adverse events, infection events and SREs were presented in Figure 6. The funnel plots did not show obvious asymmetry, and only one study (Fizazi, Karim 2011) evaluating the incidence of serious adverse events laid outside the limits of the 95% CI. Considering that the accuracy of funnel plots might be limited by the small number of studies, we complemented the Egger’s test to statistically examine the publication bias. The Egger’s test suggested no significant publication bias for the incidence of adverse events (P=0.310), serious adverse events (P=0.713), infection events (P=0.388) and SREs (P=0.554).

Figure 6 Funnel plots for the incidence of adverse events (a), serious adverse events (b), infection events (c) and SREs (d).
Discussion

We obtained several major findings from the present meta-analysis based on data from 21042 patients with bone-related diseases. From an efficacy perspective, Dmab resulted in less SREs in patients with bone metastases compared with ZA. For medication safety, Dmab significantly reduced the overall rate of adverse events including severe adverse events compared with ZA. Moreover, Dmab did not induce a higher risk of infection.

The benefit of preventing SREs in patients with bone metastases achieved by Dmab was consistently reported across included clinical trials with no interstudy heterogeneity. Previous meta-analyses have also confirmed the advantage of Dmab over ZA in delaying the onset of SREs\(^{21-23}\). SREs secondary to bone metastases such as pathological fracture, spinal cord compression, radiation or surgery to bone commonly occur clinically\(^{28}\), resulting in reduced survival, higher functional independence rates and dramatically lower health-related quality of life\(^{29}\). Moreover, SREs impose considerable financial burden on patients due to subsequent treatments\(^{30,31}\). Despite that the direct drug cost for Dmab was higher than ZA, it can be remarkably offset by reduced costs contributed by preventing or delaying the onset of SREs\(^{19,20}\). Therefore, compared with ZA, Dmab can alleviate both the health and economic burden for patients.

The comparison of the overall adverse events rate between Damb and
ZA has been little evaluated in the previous meta-analysis. After processing data from ten RCTs which enrolled a total of 15207 patients, our analyses indicated that Dmab was superior to ZA in declining the overall rate of adverse events. Of the ten studies, three included patients with multiple myeloma\textsuperscript{8,10,32} and two included patients with postmenopausal osteoporosis\textsuperscript{5,18}, which relatively well represented the spectrum of indications of antiresorptive regents. Of note, no adverse events were recorded in Dmab group in one study based on patients with postmenopausal osteoporosis\textsuperscript{5}, which was also the major source of heterogeneity. One potential explanation was that all patients underwent previous treatment of Dmab with a mean duration of 2.2 years before the start of the trial and were thus well tolerated to a second course of Dmab treatment. After excluding this study for sensitivity analysis, the result remained significant with a remarkable decrease in heterogeneity (P=0.020, I\textsuperscript{2}=0).

Moreover, Dmab was also associated with fewer serious adverse events after evaluating data from nine clinical trials. A Previous meta-analysis based on patients with bone metastases demonstrated that Dmab administration was associated with lower risk of serious adverse events including hypocalcaemia, new primary malignancy and particularly renal toxicity\textsuperscript{16}, which together with the result of ours, confirmed that Dmab had advantages in reducing the occurrence of serious adverse events over ZA.
RANKL pathway is expressed in activated lymphocytes and is involved in the formation of lymphoid nodes and thymic microenvironment\textsuperscript{33,34}, and its inhibition by Dmab was concerned to be correlated with a higher risk of infection. As shown by our analysis result, Dmad did not significantly increase the incidence of infection event compared with ZA. However, according to pooled estimate of four included clinical trials, the overall rate of infection after infusion of Dmab was 36.2%. Additionally, serious and opportunistic infections have been observed, though rarely, in patients treated with Dmab\textsuperscript{35,36}. Therefore, Dmab-induced infection still merit consideration before the initiation of therapy.

The present meta-analysis provided an assessment of current evidence regarding the efficacy and safety of Dmab versus ZA based on 13 high-quality RCTs which covered several bone-related diseases. To our current knowledge, compared with previous studies regarding the related topic, this meta-analysis contains the largest number of RCTs and covers the widest range of bone-related diseases, contributing to a reliable result and a more extensive application of analysis results. Despite these strengths, our study has several limitations. Even though the studies included in our meta-analysis were not confined to bone metastases, the number of studies evaluating non-cancer diseases such as postmenopausal osteoporosis was too small to conduct a reliable and robust subgroup analysis, which may limit the generalization of our results. For osteoporosis, the results must be
interpreted with caution, and a subgroup analysis is warranted with more articles published. Also, some included studies were sponsored by pharmaceutical companies and as such they were not free of potential pharmaceutical company bias.

**Conclusion**

Based on 13 high-quality randomized clinical trials, our results demonstrated that denosumab was superior to zoledronic acid in reducing the overall rate of adverse events as well as serious adverse events, and in reducing the onset of SREs. The treatment of denosumab was not correlated with a higher risk of infection as previously concerned. Considering the superiority of denosumab in safety outcomes, denosumab will be regarded as an optimal intervention for bone-related diseases. However, for other bone-related diseases rather than bone metastases, the superior safety of denosumab should be generalized with caution and further analyses are still warranted.

**Declarations:**

**Ethical Approval**

Not applicable

- **Consent to Publish**

We exceedingly hope that this manuscript could be accepted and published.

- **Authors Contributions**
Study design: LWH; Literature search: LWH, JRY; Study selection: LWH; Study draft and revision: LWH, JRY, FZY, YSJ and ZJ; Article guarantor: Dr. LI Ye

-Funding
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-Competing Interests
Not applicable

-Availability of data and materials
Not applicable

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**Figure Legends**

Figure 1 A flow diagram of the literature search

Figure 2 Forest plot for the incidence of adverse events in denosumab compared with zoledronic acid

Figure 3 Forest plot for the incidence of serious adverse events in denosumab compared with zoledronic acid

Figure 4 Forest plot for the incidence of SREs in denosumab compared with zoledronic acid

Figure 5 Forest plot for the incidence of infection events in denosumab compared with zoledronic acid

Figure 6 Funnel plots for the incidence of adverse events (a), serious adverse events (b), infection events (c) and SREs (d)
| Year | Country | Design | D group | Z group |
|------|---------|--------|---------|---------|
|      |         |        | Patients Number | Median Age | Male percentage | Patients Number | Median Age | Male percentage |
| 2010 | America | RCT    | 1026    | 57       | 0.8%        | 1020    | 56       | 0.9%        |
| 2011 | America | RCT    | 886     | 60       | 66.0%       | 890     | 61       | 62.0%       |
| 2011 | France  | RCT    | 950     | 71       | 100.0%      | 951     | 71       | 100.0%      |
| 2012 | Italy   | RCT    | 411     | 60       | 74.0%       | 400     | 61       | 68.0%       |
| 2012 | America | RCT    | 886     | 60       | 66.0%       | 890     | 61       | 62.0%       |
| 2012 | Spain   | RCT    | 1026    | 57       | 0.8%        | 1020    | 56       | 0.9%        |
| 2014 | America | RCT    | 800     | 59       | 66.0%       | 797     | 61       | 62.0%       |
| 2015 | France  | RCT    | 950     | 71       | 100.0%      | 951     | 71       | 100.0%      |
| 2015 | Germany | RCT    | 1912    | 58       | 31.0%       | 1910    | 59       | 29.0%       |
| 2016 | America | RCT    | 321     | 68.5     | 0.0%        | 322     | 69.5     | 0.0%        |
| 2018 | America | RCT    | 859     | 63       | 54.0%       | 859     | 63       | 55.0%       |
| 2018 | Greece  | RCT    | 30      | 64.8     | 0.0%        | 27      | 65.2     | 0.0%        |
| 2016 | America | RCT    | 325     | 56       | 0.0%        | 342     | 55.9     | 0.0%        |
|      |         |        | 153     | 70       | 100.0%      | 128     | 71       | 100.0%      |
| Year | Country | Design | D group | Z group |
|------|---------|--------|---------|---------|
|      |         |        | Patients Number | Median Age | Male percentage | Patients Number | Median Age | Male percentage |
| 2010 | America | RCT    | 1026    | 57      | 0.8%          | 1020    | 56      | 0.9%          |
| 2011 | America | RCT    | 886     | 60      | 66.0%         | 890     | 61      | 62.0%         |
| 2011 | France  | RCT    | 950     | 71      | 100.0%        | 951     | 71      | 100.0%        |
| 2012 | Italy   | RCT    | 411     | 60      | 74.0%         | 400     | 61      | 68.0%         |
| 2012 | America | RCT    | 886     | 60      | 66.0%         | 890     | 61      | 62.0%         |
| 2012 | Spain   | RCT    | 1026    | 57      | 0.8%          | 1020    | 56      | 0.9%          |
| 2014 | America | RCT    | 800     | 59      | 66.0%         | 797     | 61      | 62.0%         |
| 2015 | France  | RCT    | 950     | 71      | 100.0%        | 951     | 71      | 100.0%        |
| 2015 | Germany | RCT    | 1912    | 58      | 31.0%         | 1910    | 59      | 29.0%         |
| 2016 | America | RCT    | 321     | 68.5    | 0.0%          | 322     | 69.5    | 0.0%          |
| 2018 | America | RCT    | 859     | 63      | 54.0%         | 859     | 63      | 55.0%         |
| 2018 | Greece  | RCT    | 30      | 64.8    | 0.0%          | 27      | 65.2    | 0.0%          |
| 2016 | America | RCT    | 325     | 56      | 0.0%          | 342     | 55.9    | 0.0%          |
|      |         |        | 153     | 70      | 100.0%        | 128     | 71      | 100.0%        |
Additions for Table 1

| References                        | Year | Country  | Design | D group                     | Z group                     |
|-----------------------------------|------|----------|--------|-----------------------------|-----------------------------|
| Stopeck, Alison T                 | 2010 | America  | RCT    | 120mg q4w s.c               | 4mg q4w ivgtt               |
| Henry, David H                    | 2011 | America  | RCT    | 120mg q4w s.c               | 4mg q4w ivgtt               |
| Fizazi, Karim                     | 2011 | France   | RCT    | 120mg q4w s.c               | 4mg q4w ivgtt               |
| Scaglioni, Giorgio Vittorio       | 2012 | Italy    | RCT    | 120mg q4w s.c               | 4mg q4w ivgtt               |
| Vadhan-Raj, S                     | 2012 | America  | RCT    | 120mg q4w s.c               | 4mg q4w ivgtt               |
| Martin, Miguel                    | 2012 | Spain    | RCT    | 120mg q4w s.c               | 4mg q4w ivgtt               |
| Henry, David                      | 2014 | America  | RCT    | 120mg q4w s.c               | 4mg q4w ivgtt               |
| Smith, Matthew R                  | 2015 | France   | RCT    | 120mg q4w s.c               | 4mg q4w ivgtt               |
| Diehl, Ingo J                     | 2015 | Germany  | RCT    | 120mg q4w s.c               | 4mg q4w ivgtt               |
| Miller, P. D                      | 2016 | America  | RCT    | 60mg q6m twice, s.c         | 5mg once ivgtt              |
| Raje, Noopur                      | 2018 | America  | RCT    | 120mg q4w s.c               | 4mg q4w ivgtt               |
| Anastasilakis, Athanasios D       | 2018 | Greece   | RCT    | 60mg q6m twice, s.c         | 5mg once ivgtt              |
| Stopeck, Alison T                 | 2016 | America  | RCT    | 120mg q4w s.c               | 4mg q4w ivgtt               |

Notes: 120mg q4w s.c means 120 mg subcutaneously every 4 weeks; 4mg q4w ivgtt means 4 mg intravenous every 4 weeks.
| Year | Country | Design | Primary Disease |
|------|---------|--------|-----------------|
| 2010 | America | RCT    | Advanced breast cancer with bone metastases |
| 2011 | America | RCT    | Advanced cancer or multiple myeloma with bone metastases |
| 2011 | France  | RCT    | Castration-resistant prostate cancer with bone metastases |
| 2012 | Italy   | RCT    | Lung cancer with bone metastases |
| 2012 | America | RCT    | Advanced cancer or multiple myeloma with bone metastases |
| 2012 | Spain   | RCT    | Advanced Breast Cancer |
| 2014 | America | RCT    | Advanced solid tumor with bone metastases |
| 2015 | France  | RCT    | Castration-resistant prostate cancer with bone metastases |
| 2015 | Germany | RCT    | Advanced breast cancer and other solid tumours (excluding breast or prostate cancer) or multiple myeloma with bone metastases |
| 2016 | America | RCT    | Postmenopausal osteoporosis |
| 2018 | America | RCT    | Multiple myeloma |
| 2018 | Greece  | RCT    | Postmenopausal osteoporosis |
| 2016 | America | RCT    | Advanced breast with bone metastases Castration-resistant prostate cancer with bone metastases |
Table 2 Quality assessments of randomized controlled trials enrolled in the meta-analysis

| Reference                        | Item I | Item II | Item III | Item IV | Item V | Item VI | Item VII | Item VIII | Item IX | Item X | Item XI | Total Score |
|----------------------------------|--------|---------|----------|---------|--------|---------|----------|-----------|---------|-------|---------|-------------|
| Athanasios D Anastasilakis et al | 1      | 1       | 1        | 1       | 1      | 1       | 1        | 1         | 1       | 1     | 1       | 11          |
| Noopur Raje et al                 | 1      | 1       | 1        | 0.5     | 1      | 1       | 1        | 1         | 1       | 1     | 1       | 10.5        |
| PD Miller et al                   | 1      | 0.5     | 1        | 0       | 1      | 1       | 1        | 1         | 0.5     | 1     | 1       | 10          |
| Alison T. Stopeck et al           | 1      | 1       | 1        | 1       | 1      | 1       | 1        | 1         | 1       | 1     | 1       | 11          |
| Ingo J. Diel et al                | 1      | 1       | 0.5      | 0.5     | 1      | 0       | 1        | 1         | 0.5     | 1     | 1       | 8.5         |
| M. R. Smith et al                 | 1      | 1       | 0.5      | 1       | 1      | 1       | 1        | 1         | 0.5     | 1     | 1       | 10          |
| David Henry et al                 | 1      | 1       | 1        | 1       | 1      | 1       | 1        | 1         | 1       | 1     | 1       | 11          |
| Giorgio Vittorio Scagliotti et al | 1      | 0.5     | 1        | 1       | 1      | 1       | 1        | 1         | 1       | 1     | 1       | 10.5        |
| Miguel Martin et al               | 1      | 1       | 1        | 1       | 1      | 1       | 1        | 1         | 1       | 1     | 1       | 11          |
| S. Vadhan-Raj et al               | 1      | 1       | 1        | 0.5     | 1      | 1       | 1        | 1         | 1       | 1     | 1       | 10.5        |
| Karim Fizazi et al                | 1      | 1       | 1        | 1       | 1      | 1       | 1        | 1         | 1       | 1     | 1       | 10.5        |
| David H. Henry et al              | 1      | 1       | 1        | 1       | 1      | 1       | 1        | 1         | 1       | 1     | 1       | 11          |
| Alison T. Stopeck et al           | 1      | 1       | 1        | 1       | 1      | 1       | 1        | 1         | 1       | 1     | 1       | 11          |
## Supplementary Table 1 Critical Appraisal Skills Programme (CASP) Checklist

| Item Number | Items of quality assessment                                                                 |
|-------------|---------------------------------------------------------------------------------------------|
| 1           | Was the assigned treatment adequately concealed before allocation?                           |
| 2           | Were the outcome of patients who withdrew described and included in the analysis (intention to treat)? |
| 3           | Were the outcome assessors blinded to the treatment status?                                  |
| 4           | Were the treatment and control groups comparable at entry?                                    |
| 5           | Were the participants blinded to the assignment status after allocation?                      |
| 6           | Were the treatment providers blind to the assignment status?                                 |
| 7           | Were the care programs, other than the trial options, identical?                              |
| 8           | Were the inclusion and exclusion criteria clearly defined?                                    |
| 9           | Were the interventions clearly defined?                                                       |
| 10          | Were the outcome measures used clearly defined?                                               |
| 11          | Were diagnostic tests used in the outcome assessment clinically useful?                       |