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MASTER THESIS

A SYSTEMATIC REVIEW OF INTERVENTIONAL STUDIES ASSESSING THE USE OF BIPHOSPHONATES IN MULTIPLE MYELOMA

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ΠΕΡΙΛΗΨΗ

Εισαγωγή: Τα διφωσφονικά (ΔΦ) είναι φάρμακα που χρησιμοποιούνται για την πρόληψη επιπλοκών από το μυοσκελετικό σύστημα ατόμων με πολλαπλούν μυέλωμα (ΠΜ)

Σκοπός: Η συστηματική ανασκόπηση της βιβλιογραφίας σχετικά με την ασφάλεια και την αποτελεσματικότητα των διφωσφονικών σε ασθενείς με ΠΜ.

Υλικό & Μέθοδος: Πραγματοποιήθηκε συστηματική ανασκόπηση της βιβλιογραφίας, για κλινικές δοκιμές που εξετάζουν τη χρήση ΔΦ σε ασθενείς με ΠΜ. Συμπεριλήφθηκαν μελέτες όπου συγκρίνονταν κάποιο ΔΦ με εικονικό φάρμακο/ άλλο ΔΦ/ κανένα ή δενοσουμάμπη (ΔΣ) σε σχέση με την αποτελεσματικότητας τους ως προς την επιβίωση, την εξέλιξη ης νόσου, την εμφάνιση οστικών επιπλοκών, και την ασφάλεια της χρήσης τους.

Αποτελέσματα: Από 1003 μελέτες που ανασύρθηκαν, 49 χρησιμοποιήθηκαν για ποιοτική σύνθεση. Το ζολεδρονικό οξύ (ΖΟ) μείωσε τις οστικές επιπλοκές, βελτίωσε την επιβίωση και διεύρυνε το διάστημα επιβίωσης χωρίς εξέλιξη σε σχέση με την κλοδρονάτη (ΚΛ), κατά 5.5 και 2 μήνες αντίστοιχα. Μικτά ήταν τα αποτελέσματα σχετικά με την αποτελεσματικότητα της παμιδρονάτης (ΠΑΜ) στις οστικές επιπλοκές. Την βέλτιστη ασφάλεια επέδειξε η ΚΛ σχετικά με την οστεονέκρωση της γνάθου. Η δοσολογία των ΔΦ με ενδοφλέβια χορήγηση πρέπει να προσαρμόζεται ανάλογα με τη νεφρική λειτουργία. Η ΔΣ ήταν ισοδύναμη με το ΖΟ στην επιβίωση και την ελάττωση σκελετικών επιπλοκών και επέκτεινε το διάστημα ελεύθερο νόσου.

Συμπέρασμα: Τα ΔΦ έχουν καθιερωθεί πλέον στην αντιμετώπιση του ΠΜ, με αποτελεσματικότητα στην ελάττωση οστικών συμβαμάτων και ασφάλεια σε μακροχρόνια χορήγηση. Νεότερης γενεάς φάρμακα κερδίζουν έδαφος και ενδεχομένως να τα αντικαταστήσουν στο μέλλον.

Λέξεις Κλειδιά: συστηματική ανασκόπηση, διφωσφονικά, πολλαπλούν μυέλωμα, ζολεδρονικό οξύ, δενοσουμάμπη, παμιδρονάτη, κλοδρονάτη

ABSTRACT

Introduction: Biphosphonates (BP) due to their ability to inhibit osteoclast activity, are used to prevent skeletal complications from multiple myeloma (MM).

Objective: To review the literature regarding the efficacy and safety of BP in MM patients.

Methods: The literature was systematically searched for interventional studies assessing the use of BP in MM patients. Included studies were those that any type of BP was compared to placebo (PLC), no treatment (NT), other bisphosphonate or denosumab (DENOS). Overall survival (OS), disease progression (DP), skeletal related events (SREs), bone pain (P), osteonecrosis of the jaw (ONJ) and renal toxicity (RT) were the outcomes of interest.

Results: A total of 1003 studies were retrieved and 49 were used for qualitative synthesis. ZOL was more effective than CLOD in reducing SREs, improving progression free survival (PFS) and OS by 2 and 5.5 months respectively. Results are mixed regarding the efficacy of PAM in reducing SREs. ONJ rates were higher for ZOL, but under 5%, with CLOD having the safest profile. For BPs administered intravenous (IV), dose adjustments should be made according to renal function. DENOS demonstrated non-inferiority to ZOL for OS & reduction of SREs but was more effective in improving PFS.

Conclusion: Biphosphonates are established drugs in the treatment of MM, with a good safety profile for long-term administration. Newer drugs, are gaining ground and may even replace them in the treatment of MM

Keywords: bisphosphonate, multiple myeloma, systematic, zoledronic, pamidronate, clodronate, review, denosumab

ABBREVIATIONS

BMSc	Bone Mesenchymal Cells
RANKL	Receptor Activator of Nuclear Factor Kappa-b Ligand
BP	Biphosphonates
ETI	Etidronate
CLO	Clodronate
PAM	Pamidronate
ZOL	Zoledronic acid
IBA	Ibandronate
MM	Multiple Myeloma
MGUS	Monoclonal Gammopathy of Unknown Significance
PO	Per Os (orally)
IV	Intravenous
ONJ	Osteonecrosis of the Jaw
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
MeSH	Medical Subject Headings
RCTs	Randomized Controlled Trials
PLC	Placebo
DP	Disease Progression
SREs	Skeletal Related Events
OS	Overall Survival
PFS	Progression Free Survival
TTDP	Time to Disease Progression
TTSRE	Time to Skeletally Related Event
RT	Renal Toxicity
VC	Vasiliki Chatziravdeli
GK	George Katsaras
MD	Median
IQR	Interquartile range
NT	No Treatment
OBS	Observation

OR	Odds ratio
HR	Hazard Ratio
CI	Confidence Interval

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A. INTRODUCTION

Multiple myeloma (MM) is a malignant disease of the haemopoietic system, characterized by plasma cell proliferation contained mainly in the bone marrow, but can also present outside, as solitary plasmacytoma. It is a heterogenous condition, that can vary from monoclonal gammopathy of unknown significance to plasma cell leukemia.(1,2) It mainly affects people who are between their sixth and seventh decade of life, although 37% of cases involve people younger than that. It is rarely encountered in age groups younger than 30 years old.(1,3) Multiple myeloma in the primary stages, manifests as a premalignant condition without end organ involvement, characterized as monoclonal gammopathy of unknown significance (MGUS) and smoldering myeloma.(1) Skeletal involvement is disease-defining and correlates with disease progression, tumor burden and prognosis.(4) It is estimated that 85% of asymptomatic patients with MM have osteopenia to some extent.(3)

MM-induced bone disease interferes with normal bone remodeling, causing excessive differentiation and activation of osteoclasts, thus turning the balance towards bone resorption.(5) Interaction between MM cells and bone mesenchymal cells (BMSc) leads to expression of receptor activator of nuclear factor Kappa-b ligand (RANKL) from osteoblasts, which stimulates osteoclast differentiation and activation.(6)

Biphosphonates (BPs) are a diverse group of molecules that inhibit osteoclast activity by binding to hydroxyapatite crystals. After their absorption to bone surface and internalization by osteoclasts they interfere with their function and cause apoptosis.(7,8) Their core structure consists of two phosphonate groups that bind with a carbon atom and are very stable in biologic environment. Biphosphonates are classified according to whether they are nitrogen containing or not, which correlates with their potency. First generation non-nitrogen BPs are etidronate (ETI) and clodronate (CLOD), second generation nitrogen-containing are pamidronate (PAM) and ibandronate (IBA) and third generation nitrogen-containing are zoledronic acid (ZOL), who are worth mentioning among others. Nitrogen-containing BPs are 10-10000 times more potent than non-nitrogen, regarding anti-resorption ability.(8–10) They can be administered either orally (PO) or intravenous (IV), but they are poorly absorbed from the gastrointestinal tract and therefore require very careful administration to maximize absorption.(11,12) Based on in

vitro data ETI is regarded the least potent and ZOL the most potent BP.(10,13) Side effects that have been recorded from their use include esophageal irritation/ulceration,(14) renal function impairment, hypocalcemia and the more rare but severe osteonecrosis of the jaw (ONJ).(15–17)

For their anti-resorptive action they have become important adjuvant agents to the treatment of malignancies that cause bone destruction such as MM, among others.

The aim of this systematic review is to assess the use of BPs in the treatment of MM, as demonstrated by interventional studies from 1980 up to date and demonstrate the benefits and potential harms that arise from their use.

B. METHODS

The methods and the results of this review have been carried out in accordance with the principles of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)(18).

Search strategy

A systematic search of the literature was conducted in the databases of National Library of Medicine- Pubmed.gov, Scopus, Web of Science and Clinicaltrials.gov for relevant studies. We used keywords through evaluation of Medical Subject Headings (MeSH) which were: bisphosphonates, diphosphonates, zoledronic, pamidronate, alendronate, risedronate, etidronate, zoledronic acid, risedronic acid, multiple myeloma, plasma cell myeloma and limited our search criteria to include clinical trials and randomized controlled trials (RCTs) in humans were that was applicable. The search was concluded on August 9th, 2021. Detailed search strategy per database is included in Appendix.

Selection criteria

Inclusion criteria consisted of interventional studies (clinical trials, RCTs) that compared bisphosphonates versus placebo/no treatment/other bisphosphonates/denosumab(19) in multiple myeloma patients, who were receiving standard chemotherapy treatment or not, according to their disease stage. Eligible studies should include at least one outcome of interest. Studies with small sample size were also included. Studies that included patients with MM and other metastatic tumors in the population were also included and when subgroup data were available, only the MM patients were considered. Regarding large RCTs with multiple publications, all studies reporting different outcomes or subgroup analysis publications, that came from the same sample were included.

Exclusion criteria consisted of observational studies, case reports, case series, Phase I/II pharmacokinetic and dose-determination studies, in vitro studies, animal studies, studies with no full text available or studies where the full text could not be retrieved even after communication with the authors, articles with no full text published in English, studies that were not conducted in the population of interest but in humans with other

types of tumors with metastatic bone disease and studies that did not include even one of the outcomes of interest.

Types of participants

Participants who were diagnosed with MM, as this was defined by researchers in each study. There were no uniform criteria among studies, but they were in accordance with the official diagnostic criteria for MM, that were in effect during the study period. Participants with asymptomatic to advanced MM were included.

Types of interventions

Intervention group: Biphosphonate or denosumab

Control group: Placebo (PLC) or no treatment or other bisphosphonate

Types of Outcomes

Primary outcomes

Disease progression (DP)-As they were defined by the authors of each study. There were no uniform criteria in all included studies. Some assessed DP using the International Response criteria(20) and others by clinical, radiographic and/or biochemical evaluation. In some studies DP was reported as progression free survival (PFS) or as time to disease progression (TTDP) or as time to first skeletal related event (TTSRE).

Overall survival (OS)-In terms of mortality

Skeletal related events (SREs)- As they were defined by authors of each study. This could include participants experiencing new osteolytic lesions, pathological vertebral or non-vertebral fractures, loss of vertebral height, spinal cord compression or hypercalcemia.

Secondary outcomes

Reduction in bone pain

Number of participants with osteonecrosis of the jaw (ONJ)

Renal toxicity (RT) Grade III/IV(National Cancer Institute common toxicity criteria)

Study selection

Two reviewers (VC and GK) independently conducted the literature search according to the prespecified criteria. Duplicate results were removed manually at the initial stage

and the rest of the results were screened for eligibility by Title & Abstract. In the final stage, the full text of the remaining studies was assessed for inclusion. When it was not possible to find full text of a study, the authors were contacted. Studies approved by at least one of the reviewers was considered eligible.

Data Extraction

Data extraction was done by VC and approved by GK. For all studies we extracted the following data: the name of the first author, year of publication, type/mane of study, the population characteristics, number of participants, type of intervention drug, type of comparator drug, the dosage, route and frequency of administration of the intervention drug, treatment duration, follow up duration and outcome measures.

Data analysis

Data were imported in Excel spreadsheet, Microsoft Office 365. Results were reported as hazard ratio (HR), odds ratio (OR) or descriptively by means of percentages or number of events with the attributed p-value, were that was available.

Risk of bias assessment

In order to assess the risk of bias (methodological quality) of each study included in the review we used the revised Cochrane risk-of-bias tool for randomized trials (RoB2).(21) A fixed set of domains of bias (bias arising from randomization process, bias from deviations to the intended interventions, bias from missing data, bias from measurement of the outcome, bias from selection of the reported result) focusing on different aspects of trial design, conduct, and reporting were assessed. Two independent reviewers (VC and GK) evaluated the included articles, and any discrepancies were resolved through discussion.

C. RESULTS

Search results

Our original search yielded 1003 results. Ninity-five full text studies were screened after duplicates and studies from Title & Abstract were removed. The final number of studies that were eligible for qualitative synthesis after full text assessment were 48. Detailed diagram of the process with reasons for exclusion is illustrated in Appendix.

Study Characteristics

There were 22 studies regarding ZOL with a total number of 6103 participants receiving the drug.(22–39) For PAM we found 13 studies with 2224 participants.(22,40–50) 16 studies for CLOD with 3828 participants,(51–67) 2 for IBA (49,68) and 1 for ETI.(69) Details are presented in Table 1

As far as population characteristics is concerned, 7 studies included participants with MM and other metastatic solid tumors, namely breast, prostate cancer and others.(22,23,26,28,32,35,37) The rest of the studies had participants with MM only, in various stages. In 30 studies it was specified that participants should not have received bisphosphonate treatment prior to study entry for a duration ranging from 1-6 months to none at al. Details on population and study characteristics is provided in Table 2.

Regarding comparisons between bisphosphonates there were 9 studies comparing CLOD with placebo, no treatment or chemotherapy only,(53–59,65–67). Three were published results of the same trial.(54,57,67) Six studies compared CLOD with ZOL.(51,52,60–63) These 6 studies were published results from a single large RCT. For PAM there were 9 studies comparing it with placebo/chemotherapy only or observation. (43–48,50,70,71) There was 1 study comparing PAM, PAM and thalidomide and placebo (40) and one single arm trial.(42) Finally there were two studies comparing PAM to different doses of ZOL.(22,23) Regarding ZOL there were 6 studies comparing it to denosumab. Three were part of the same large RCT,(29–31) two part of another (35,37) and one more study.(25) Two studies compared ZOL in different doses with PAM as mentioned before, one compared different infusion times,(36) one different intervals of infusion(26) and two were single arm trials. The rest involved ZOL versus placebo, no treatment or only chemotherapy (Table 2).

Administration of ZOL was intravenous (IV)/every 4 weeks in most studies. CLOD was orally (PO) in various doses from 100mg/daily in older studies to 2.4g/daily. The prevalent dose of CLOD in more recent studies was 1600mg/daily. Finally, the prevalent dose of PAM was 90mg (IV)/every 4 weeks (Table 2).

Risk of Bias Assessment

The results from the risk of bias assessment of the included studies are presented in Figure ***2*** and Figure 3. Twenty-seven RCTs were assessed. There were some concerns arising from the randomization process, because detailed information about how the randomization was done, was not provided in a lot of studies. Furthermore, increased bias arose in the selection of reported results section, because of the use of many different measures in order to evaluate the outcomes. Lastly, in most of the studies there was no problem with missing data or protocol deviations.

Outcome measures

Primary outcomes: Disease progression, overall survival and skeletal related events

CLOD vs PLC/ZOL

Studies regarding the use of CLOD date from 1980 to 2013, with the most recent being a large multicenter RCT, the Medical Research Council Myeloma IX study, with 1960 total number of participants.(63) Five studies reported outcomes from this trial with median (MD) follow up of 3.7 years (IQR 2.9-4.7), which was extended to 5.9 years.(52,60–63) In this study CLOD was compared to ZOL and patients were further stratified to intensive and non-intensive pathway, according to intensity of induction to chemotherapy, and received two different chemotherapy combinations in each pathway. ZOL was superior to CLOD in increasing overall PFS by 2 months, (HR 0.88;95% CI,0.80–0.98), but when the same outcome was assessed separate for the intensive and non-intensive pathway, it did not reach statistical significance (HR 0.90;95% CI, 0.78–1.05 and HR 0.87;95% CI, 0.74–1.01 respectively). Overall survival was 44.5 months for CLOD and 50 months for ZOL, which was significant (HR 0.84;95% CI, 0.74–0.96). 27% of patients in the ZOL group had a SRE before disease progression, compared to 35% (p=0.0004).(63) In the intensive pathway, in both subgroups, ZOL reduced the risk of SREs significantly compared to CLOD (27.9% vs 36.3% p=0.017). Overall ZOL reduced SREs compared to CLOD, in patients receiving bisphosphonates for more than 2 years (p=0.0102), regardless of other

treatment regiments.(61) In the extended follow up, results demonstrated a significant increase in PFS as well as OS (HR 0.89;95% CI, 0.80–0.98 and HR 0.86;95% CI,0.77– 0.97 respectively), increasing OS by 5.5 months. In the intensive pathway, there was no significant difference in PFS and OS between groups receiving different induction to chemotherapy. In the non-intensive pathway OS was similar between the two groups but PFS was better in the group that received thalidomide agent as well(CTD) (HR, 0.81; 95% CI, 0.69–0.94).(52) Subgroup analysis of transplant eligible patients in the Myeloma IX study demonstrated that ZOL was not superior to CLOD in OS for patients with complete response (CR) to therapy, but significantly improved OS in patients with PR (HR 0.53 [95% CI, 0.32-0.86]). ZOL was marginally better than CLOD in reducing SREs only in patients with very good partial response (VGPR) (HR 0.74;95% CI, 0.52-1.05) and not in those with CR.(60)

There were two more large RCTs, one from the Finnish Leukemia Group(57) and the VIth MRC Multiple Myeloma Trial (65), each with two publications recruiting a total number of 871 participants, comparing CLOD with placebo (PLC). In those studies, there was no significant difference in OS, with a follow up, up to 8 years. CLOD was effective in preventing bone progression and reduced osteolytic lesions significantly (p=0.026), but no difference was noted between groups regarding vertebral and non-vertebral fractures. Riccardi et al (55) and Heim et al (53) also demonstrated significant improvement in bone progression with CLOD, as well as survival.(55) Finally, the studies of Siris et al (59) and Delmas et al (58) reported less osteolytic lesions compared to PLC at 6 and 12 months, but had very few participants. Details are provided in Table 3.

PAM vs PLC/No Treatment (NT)/Chemotherapy (CHEMO)/ZOL/IBA/PAM

Eleven studies, from 1996-2011, were retrieved where PAM was evaluated in MM patients with a total number of 2224 participants.(22,40,43–49) PAM versus PLC/NT or only CHEMO demonstrated no significant difference in OS. In four studies that included patients newly diagnosed with or without osteolytic lesions, SREs were reduced(42,47,49,51) but the same was not evident in the studies of Brincker et al, Attal et al, Kraj et al and Terpos et al.(40,41,43,71) The later included asymptomatic or participants in the plateau phase. When compared to ZOL there was no difference in reducing SREs(22,23) and the same was demonstrated in DP when compared to IBA (Table 3).(49)

ZOL vs PLC/NT/PAM/CLOD/DENOS

The efficacy of ZOL was assessed in 22 studies, from 2001-2021, with 6103 participants. In asymptomatic MM patients ZOL showed no superiority versus NT in PFS at 5 years. It reduced SREs (OR 2.9;95% CI, 1.04-8.06) but with a wide confidence interval.(34) When thalidomide (THAL) was added, in the same population type, their combination was significantly better at PFS and TTDP than ZOL alone.(39) OS and PFS was improved significantly in patients with symptomatic and advanced disease, and SREs were reduced in the ZOL group.(33,38) For patients with biochemical relapses, the projected 4-year risk for SRE was 6% versus 40% ($p<0.001$) for ZOL and NT respectively. DP was reduced significantly, but not OS (73% vs 46%, $p=0.161$ for ZOL vs NT). A marginally significant improvement in OS was noted for patients with bone lesions at entry.(24) Regarding studies comparing ZOL vs PAM or CLOD, their results have already been mentioned. Administration of ZOL with longer interval or longer infusion time had the same efficacy in reducing SREs.(26,28,36) Long-term treatment with ZOL, 4 years compared to 2 years, reduced SREs ($p<0.001$) but not OS or PFS.(27)

Lastly, we retrieved 3 trials comparing ZOL with DENOS, form 2011-2021, with 2256 participants.(27,32,37) One trial had 3 publications, with results from subgroup analysis (29–31) and another had two (35,37). OS was similar between the two drugs and TTSRE showed non-inferiority of DENOS and superiority in post hoc analysis.(25,30,35) In a large trial of Raje et al (30), PFS was significantly increased for the DENOS group by 10.5 months versus the ZOL group.(30) In a subgroup analysis of Asian patients that participated in the same study, 38.8% of patients on DENOS had first on study SRE, versus 50.5%, but it did not reach statistical significance.(29) The group that benefited the most from DENOS regarding PFS, were patients <70 years old and those with intent for autologous stem cell transplantation.(31) There was significant participant withdrawal (80%) in the trial of Henry et al, which reduced the sample size from 1776 to 358. There were differences between groups, regarding patient characteristics a demonstrated in the study of Raje et al (25). More patients with poor renal function were treated with DENOS and patients taking ZOL, had stem cell therapy and immunomodulation therapy more frequent, which may have affected time to disease progression (Table 3).

Secondary outcomes

Bone Pain

Results from 3 CLOD versus PLC studies, indicated a significant reduction of pain, in patients receiving CLOD.(53,56,65) In the largest trial of the three, at 2 years, 10.9% of patients in the CLOD group were having back pain compared to 19.9%. In the preceding study of Lahtinen et al (57) the number of patients with no pain at 2 years was 53.6% and 44.6% for CLOD and PLC respectively, which did not reach statistical significance.

In the studies of Berenson et al (44), Brincker et al (46) and Terpos et al (70) PAM was successful in reducing bone pain compared to PLC or CHEMO only. On the other hand, Kraj et al (71) demonstrated a reduction in pain from PAM administration the first 6 months and no difference after 9 months. Even though the study had only 46 participants the treatment duration was 66 months, with a long follow up period. When compared with ZOL 4mg/IV, there was 67% reduction in pain score for ZOL and 50% for PAM, with 10 months of treatment duration.(22) Patients recruited in a single arm trial for ZOL, experienced significant pain reduction from baseline in at least 4 out of 6 visits.(32) When DENOS was compared to ZOL, one study demonstrated superiority in reducing bone pain (in favor of DENOS), but had 80% participant withdrawal,(37) while in another large trial, the same result was not reproduced, with both drugs showing similar effectiveness.(30) When patients receiving ZOL for different duration, infusion time and frequency, results regarding pain did not differ (Table 4).(27,28,36)

Osteonecrosis of the jaw

In patients that were treated with PAM, the rate of ONJ was very small. In the study of Attal et al(40) only 2 of 397 participants developed ONJ after 26 months of treatment . CLOD when compared to ZOL, in the MRC MYELOMA IX study, had significantly lower incidence of ONJ, in the short and long-term follow up (0.5% versus 3.7% respectively).(51,63) The incidence of ONJ in patients treated with ZOL was less than 4% in the studies included.(24,26,28,30,35) There were two studies that reported 0 and 1 patient, but the duration of therapy was short.(32,34) Surprisingly, Aviles et al (38) reported no patient with ONJ after 2 years of ZOL administration, with a follow up ranging from 3-8 years. In two large studies comparing ZOL with DENOS there was no difference

in the incidence of ONJ, which had a range of 1.3-3% and 1.1-4% respectively (Table 4).(30,35)

Renal Toxicity

In the studies with CLOD versus PLC or CHEMO only, there were no serious events of renal toxicity between groups.(53,56,57) In the MRC MYELOMA IX study, events of acute renal failure were similar for CLOD and ZOL, with no significant difference in the short and long-term follow up.(51,63)

PAM was generally well tolerated and there was no significant toxicity compared to PLC/NT/CHEMO.(40,44–46,70,72) ZOL, in the 4mg dose, every 4 weeks with 15' of infusion time, when compared to PAM had similar safety profile.(23) In studies of ZOL versus PLC/NT/CHEMO, the percentage of serious renal impairment was low and there was no significant difference between groups.(24,26,28,32,36,38,47) When compared to DENOS, there was higher percentage of patients with adverse events regarding renal function, and that was more pronounced in participants with baseline lower creatinine clearance Table 4. Overall ZOL had a good safety profile, when the dosage was adjusted for creatinine clearance.(30,35)

There were three studies identified with IBA and ETI, that did not show significant benefit in reducing bone morbidity in MM patients ,or improve survival and disease progression (Table 4).(49,68,69)

D. DISCUSSION

In MM patients, the progression to bone disease is of pivotal importance that affects morbidity. Most patients will eventually develop skeletal lesions (80-90%) due to the imbalance between bone apposition and resorption, that follows when MM tumor burden exceeds 50% in a local area.(73) Histologic studies have demonstrated that there is increased osteoclast (OC) activity adjacent to MM cells.(73) MIP-1a is a chemokine produced by MM cells, which help them to adhere to bone marrow MSCs and stimulate production of RANKL, LI-6, TNF and vascular endothelial growth factor.(74) This in consequence causes proliferation and differentiation of OCs, which leads to increased local bone resorption and the creation of lytic lesions.

Bisphosphonates' main target is to reduce proliferation of OCs and induce apoptosis and for that reason they play an important role in the treatment of MM.(10)

Results from the study of Lahtinen et al. (57) first demonstrated that there was a beneficial effect of oral CLOD in reducing osteolytic lesions and delaying bone disease progression in MM patients. That result was also evident in the study of Berenson et al. (44), regarding IV PAM. When ZOL became available, clinical trials comparing it to PAM demonstrated similar safety profile and slightly better efficacy in reducing SREs and bone pain.(22,23) In the large MRC MYELOMA IX study,(63) ZOL proved to be superior to CLOD in increasing OS by 5.5 months and reducing SREs. Even though it had higher incidence of ONJ, that percentage was less than 5%. Renal toxicity was slightly higher for ZOL but there was no significant difference. In the future study of Himelstein et al (28), it was shown that IV 4mg ZOL administration every 12 weeks had the same efficacy, with reduced incidence of ONJ and renal function impairment, compared to every 4 weeks. Treatment with ZOL has been proven safe and effective for 2 years. The extended follow up of the MRC MYELOMA IX study showed low incidence of adverse events and the Z-MARK study, that included patients with 1-2 years of prior bisphosphonate use, extended the safe use of ZOL up to 4 years, in 3-month intervals.

A Mixed Treatment Comparison that compared the efficacy of ZOL, PAM, CLOD and IBA in reducing SREs concluded that ZOL was superior to the other BPs. In particular, ZOL had 1.43 incidence rate, while PAM had 1.64 and CLOD 1.90. The excess rates of PAM and CLOD versus ZOL in the incidence of SREs were 15% and 33% respectively.(75)

In a more recent Cochrane review and meta-analysis, bisphosphonates were effective in reducing SREs and pathologic vertebral fractures (moderate quality of evidence) but evidence for lesser bone pain was of low quality. OS was improved with ZOL but not PFS. Regarding ONJ, there was no significant difference in the incidence between BP type.(76)

Renal function deterioration is the most important complication associated with IV BP infusion. In a retrospective study, McDermott et al demonstrated that important predictive factors for renal impairment, in patients treated with ZOL, were patient age, myeloma disease, nonsteroidal anti-inflammatory drugs, cumulative doses and cisplatin therapy.(77) Caution is warranted with PAM as well, but generally doses up to 90mg every 4 weeks are well tolerated.(78) In a recent retrospective study, there was 8% incidence of

acute kidney injury in patients with pre-existing renal impairment compared to others with normal renal function.(79) Oral BPs are not associated with significant nephrotoxicity.(78)

All three bisphosphonate types have their contribution in MM treatment, but recommendations differ between various countries. American Society of Clinical Oncology (ASCO) prefers PAM in contrast to the British Committee for Standards in Hematology (BCSH) and IMWG, who favor ZOL, due to decreased incidence of ONJ and similar effectiveness. CLOD is preferred in patients that cannot attend hospital visits, but a strict intake protocol should be followed to maximize absorption.(80) All symptomatic MM patients should be started on bisphosphonates regardless of the presence or not of myeloma bone disease, but the same does not apply for smoldering myeloma.(34,47,81)

Special precautions are warranted to reduce ONJ incidence, and thorough oral examination is recommended prior to monthly IV infusion. Dental treatment before initiation of BP therapy has been associated with decreased risk of ONJ.(82,83) BP infusion should be withheld and dose adjustments are recommended in patients with impaired renal function, and specifically ZOL and PAM are not recommended in patient CrCl <30ml/min, while CLOD in CrCl <10ml/min.(80)

The development of denosumab, a human monoclonal IgG2 antibody that binds to RANKL, preventing it from activating OCs, has been tested against ZOL,(25,35) with the most recent, a large multicenter trial with 1718 participants.(30) Results from that study, with 15.8 median treatment duration, demonstrated longer progression free survival in favor of DENOS, especially in younger patients and candidates for autologous stem cell transplantation, and increased time to first skeletal related event. Furthermore, it showed non-inferiority in OS, in preventing SREs and similar safety. The incidence of hypocalcemia was more pronounced compared to ZOL, but there is no need for dose adjustments according to renal function.(84) Overall these results have led to DENOS being approved by the FDA for use in prevention of skeletally related events secondary to MM.(85)

E. CONCLUSION

Biphosphonates are established drugs in the treatment of MM, with a good safety profile for long-term administration. They are effective in reducing bone disease but are not without adverse events and limitations. The development of newer, more specific

drugs like DENOS, is gaining ground and if long term administration is proved safe and efficacious, it may even replace their use in the treatment of MM.

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85. FDA denosumab Approval.

Figure 1 PRISMA Flow Diagram

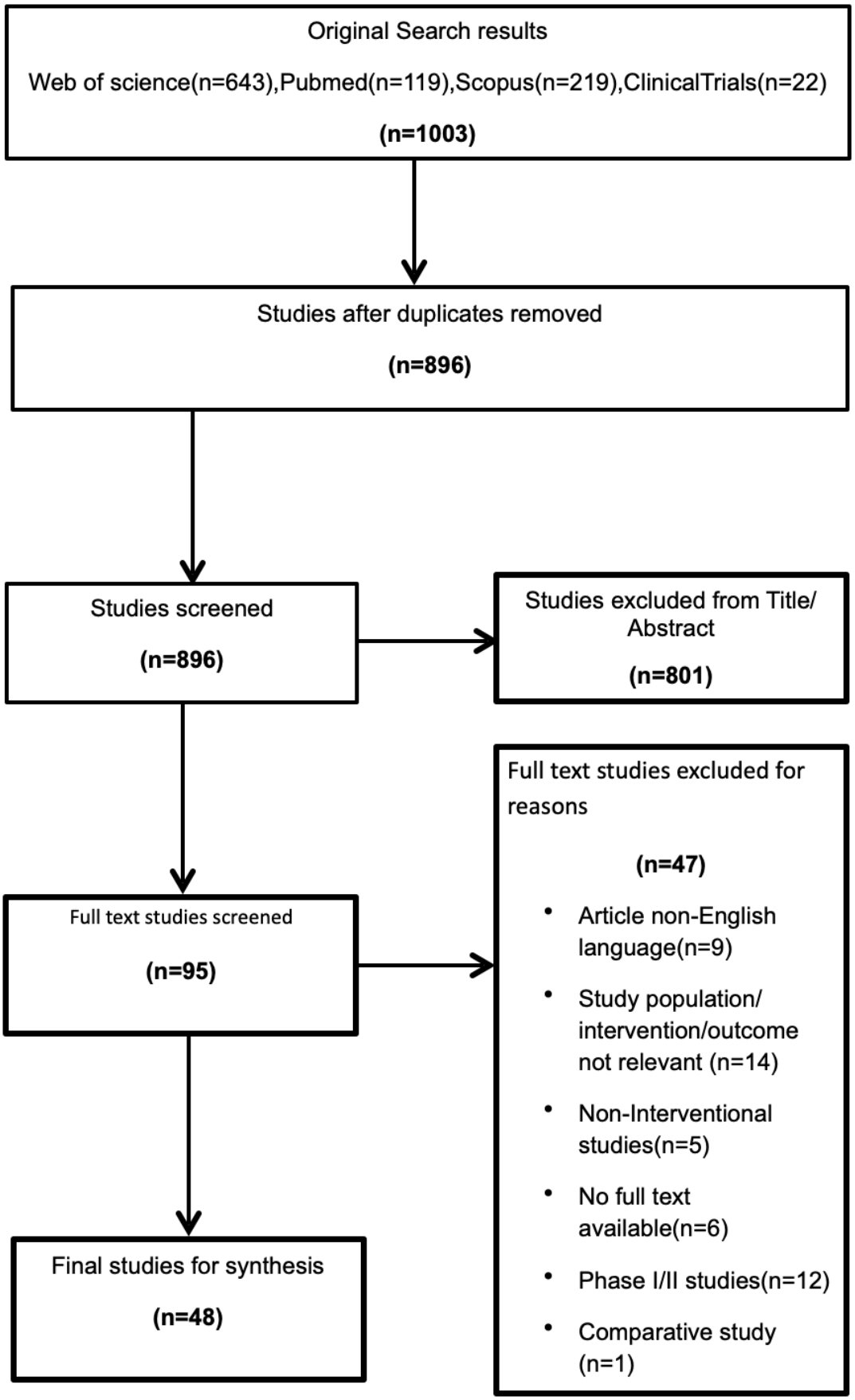


Table 1 Studies per Biphosphonate Type

Biphosphonate type	No of studies	Total No of patients	Year range
ZOL	22	6103	2001-2021
PAM	13	2224	1996-2011
CLOD	16	3828	1980-2014
IBA	2	242	2002-2003
ETI	1	166	1991

Table 2 Study Characteristics

Study ID	**Study Design**	**Population**	**Intervention/Comparator**	Study subarms	**No of Patients**	**Route,dose,frequency**	**Treatment Duration** Median (Range)	**Follow up** Median (Range)
Terpos 2021(31)	RCT Sub-group analysis (NCT01345019)	MM newly diagnosed with <1 dose of prior IV biphosphonate	DENOS+PLC (IV)	ASCT-intent. ASCT-no intent	465 394	SC, 120mg,Q4W	17.3m	42m
				Pt Age <70y Pt age>70y	602/859 257/859			
			ZOL+ PLC (SC)	ASCT-intent. ASCT-no intent	465 394	IV,4mg,Q4W	17.6m	42m
				Pt Age <70y Pt age>70y	612/859 247/859			
Huang 2020(29)	RCT Sub-group analysis (NCT01345019)	MM newly diagnosed with <1 dose of prior IV biphosphonate-Asian subgroup	DENOS+PLC (IV)		103	SC, 120mg,Q4W	15.9m(8.5-24)	17.5m(9.8-30.2)
			ZOL+ PLC (SC)		93	IV,4mg,Q4W	17.4m(9.1-26.7)	20.2m(13.1-29.2)
Raje 2018(30)	RCT (NCT01345019)	MM newly diagnosed with <1 dose of prior IV biphosphonate	DENOS+PLC (IV)		859	SC, 120mg,Q4W	15.8m (IQR 8.2-25.8)	17.3m (IQR 8.9-28.5)
			ZOL+ PLC (SC)		859	IV,4mg,Q4W	14.8m (IQR 7.5-24.9)	17.6m (IQR 9.4-28.1)
Himelstein 2017(28)	RCT (NCT00869206)	MM,BC/PC with bone lesions without receiving previous IV biphosphonates	ZOL		911 (139MM)	IV,4mg,Q4W	2y	2y
			ZOL		911 (139MM)	IV,4mg,Q12W	2y	2y
Aviles 2017(27)	RCT	MM UNTREATED	ZOL		84	IV,4mg,Q4W	48m	40.4m(23-62)
			ZOL(control)		86	IV,4mg,Q4W	24m	
Raje 2016(25)	RCT (NCT00330759)	MM or solid tumors with at least one lytic lesion	DENOS		87	SC,120mg,Q4W	N/m	17m(SD 7.8)
			ZOL		93	IV,4mg,Q4W	N/m	18.4m(SD 8)
Raje 2016(26)	RCT -ZMARK (NCT00622505)	MM already on biphhosphonates 1-2 years	ZOL		117	IV,4mg,Q4W	96w	2y
					4	IV,4mg,Q12W		
Garcia-Sanz 2015(24)	RCT -AZABACHE STUDY (NCT01087008)	MM with biochemical relapses	ZOL monotherapy		51	IV,4mg,Q4W	12 doses	38m
			None		49			

Study ID	**Study Design**	**Population**	**Intervention/Comparator**	Study subarms	**No of Patients**	**Route,dose,frequency**	**Treatment Duration** Median (Range)	**Follow up** Median (Range)
Jackson 2014(51)	RCT -MRC MYELOMA IX STUDY (ISRCTN68454111)	MM newly diagnosed without prior MM treatment except biphosphonates,low dose corticosteroids or radiotherapy	ZOL	Intensive pathway	555	IV,4mg,Q21-28D	467d (160–863)	5.9y
				Non-intensive	426		342d (154–572)	
			CLOD	Intensive pathway	556	PO,1600mg,daily	469d(174–827)	
				Non-intensive	423		323d (120–559)	
Witzig 2013(39)	RCT (NCT00432458)	Asymptomatic-Untreated MM	ZOL+THAL		35	IV,4mg,Q4W (modified later Q12W)+PO,200mg,daily		5.9y(1.5-8)
			ZOL		33	IV,4mg,Q4W(modified later Q12W)		
Aviles 2013(38)	RCT (NCT01234129)	MM UNTREATED SYMPTOMATIC	ZOL		151	IV,4mg,Q4W	24m	3-8y
			None		157			
Morgan 2013(52)	RCT -MRC MYELOMA IX STUDY (ISRCTN68454111)	MM newly diagnosed without prior MM treatment except biphosphonates,low dose corticosteroids or radiotherapy	ZOL		981	IV,4mg,Q4W	Until DP	5.9y
			CLOD		979	PO,1600mg,daily		
Larocca 2013(60)	RCT RCT -MRC MYELOMA IX STUDY-SUBGROUP ASCT (ISRCTN68454111)	MM newly diagnosed without prior MM treatment except biphosphonates,low dose corticosteroids or radiotherapy-transplant eligible patients	ZOL intensive pathway		555	IV,4mg,Q4W	Until DP	5.71y
			CLOD intensive pathway		556	PO,1600mg,daily		5.54y
Vadhan-Raj 2012(37)	RCT (NCT00330759)	ADV META SOLID TUMORS (-BC/PC)+MM without prior IV treatment with biphosphonates	DENOS+(IV) PLC		886(180 remained)	SC,120mg,Q4W	675.3 p-y	2y
			ZOL+(SC) PLC		890(178 remained)	IV,4mg,Q4W	651.9p-y	
			ZOL intensive pathway	CVAD vs CTD	555	IV,4mg,Q4W		5.9y

Study ID	**Study Design**	**Population**	**Intervention/Comparator**	Study subarms	**No of Patients**	**Route,dose,frequency**	**Treatment Duration** Median (Range)	**Follow up** Median (Range)
Morgan 2012(61)	RCT -MRC MYELOMA IX STUDY (ISRCTN68454111)	MM newly diagnosed without prior MM treatment except biphosphonates,low dose corticosteroids or radiotherapy	ZOL non-intensive pathway	MP vs CTDa	426			
			CLOD intensive pathway	CVAD vs CTD	556	PO,1600mg,daily		
			CLOD non intensive pathway	MP vs CTDa	423			
Morgan 2011(62)	RCT -MRC MYELOMA IX STUDY (ISRCTN68454111)	MM newly diagnosed without prior MM treatment except biphosphonates,low dose corticosteroids or radiotherapy-transplant eligible patients	ZOL intensive pathway	CVAD vs CTD	555	IV,4mg,Q4W	At least until DP	3.7y (IQR 2.9-4.7)
			ZOL non-intensive pathway	MP vs CTDa	426			
			CLOD intensive pathway	CVAD vs CTD	556	PO,1600mg,daily		3.8y (IQR 2.9-4.7)
			CLOD non intensive pathway	MP vs CTDa	423			
Berenson 2011(36)	Randomised open lable pilot study-ZMAX TRIAL	MM with at least one lytic lesion, without prior prolonged use of IV biphosphonates	ZOL 15' INFUSION		88	IV,4mg,Q4W	24m	12m & 24m
			ZOL 30' INFUSION		88	IV,4mg,Q4W		
Henry 2011(35)	RCT (NCT00330759)	ADV META SOLID TUMORS (-BC/PC)+MM without prior IV treatment with biphosphonates	DENOS+IV PLC		886 (180 remained)	SC,120mg,Q4W	7m (675.3p-y)	3y
			ZOL+SC PLC		890 (178 remained)	IV,4mg,Q4W	7m (651.9p-y)	
D'Arena 2011(45)	RCT	Asymptomatic MM not requiring treatment	PAM		89	IV,60-90mg,monthly	1y	5y minimum
			OBS		88			
Morgan 2010(63)	RCT -MRC MYELOMA IX STUDY (ISRCTN68454111)	MM newly diagnosed without prior MM treatment except biphosphonates,low dose corticosteroids or radiotherapy	ZOL intensive pathway	CVAD vs CTD	555	IV,4mg,Q4W	Until DP or end of study 350d(IQR 137-632)	3.7y (IQR 2.9-4.7)
			ZOL non-intensive pathway	MP vs CTDa	426			
			CLOD intensive pathway	CVAD vs CTD	556	PO,1600mg,daily	Until DP or end of study 350d(IQR 137-632)	
			CLOD non intensive pathway	MP vs CTDa	423			

Study ID	Study Design	Population	Intervention/Comparator	Study subarms	No of Patients	Route,dose,frequency	Treatment Duration Median (Range)	Follow up Median (Range)
Musto 2008(34)	RCT	Asymptomatic MM not requiring treatment	ZOL		81	IV,4mg,Q4W	1y	64.7p-m (36-72)
			OBSERV		82			
Aviles 2007(33)	RCT	MM advanced (untreated - stage III)	ZOL +CHEMO		46	IV,4mg,Q4W	24m	49.6p-m(34-72)
			CHEMO		48			
Attal 2006(40)	RCT-Inter-Groupe Francophone du Myélome (IFM)	MM with no prior treatment and one or none adverse prognostic factor	NO MAINTENANCE		200			30m(18-50)
			PAM		196	IV,90mg,Q4W		29m(19-52)
			PAM+THAL		201	IV,90mg,Q4W+PO,400mg,daily		29m(20-53)
Kraj 2004(71)	RCT	MM STAGE II-III	PAMID 60MG+CHEMO		23	IV,60mg,Q4W	66 months	6y
			CHEMO		23		66 months	
Vogel 2004(32)	CLINICAL TRIAL SINGLE ARM	MM STAGE III/other metastatic cancer types	ZOL		638(129 MM patients)	IV,4mg,Q4W	6m	6m
Terpos 2003(49)	RCT	MM NEW-Stage II without biphosphonate treatment in the previous 2 months	IBA +CHEMO		21	IV,4mg,monthly	10m	10m
			PAM+CHEMO		23	IV,90mg,Q4W		
Rosen 2003(23)	RCT	MM Advanced-Stage III/BC METAST without prior biphosphonate treatment for 12m MM stratum	ZOL 4mg		564(73 MM patients)	IV,4mg,Q4W	24M	25M
			ZOL 8mg/4mg		526(56)	IV,8/4mg,Q4W		
			PAM		558(65)	IV,90mg,Q4W		
Musto 2003(47)	RCT	MM UNTREATED stage IA or IIA	PAM		45	IV,60mg,Q4W	1y	51m(36-72)
			OBSERV		45			
Martin 2002(42)	CLINICAL TRIAL SINGLE ARM	Smoldering+indolent MM-single arm	PAM		12	IV,90mg,Q4W	12m	25m
Menssen 2002(68)	RCT	MM stage II,III without prior biphosphonate treatment 3 & 6m before study entry	IBA		99	IV,2mg, Q4W	12-24m	17m
			PLC		99			18m

Study ID	Study Design	Population	Intervention/Comparator	Study subarms	No of Patients	Route,dose,frequency	Treatment Duration Median (Range)	Follow up Median (Range)
Terpos 2001(48)	CLINICAL TRIAL	MM PLATEAU PHASE+maintenance treatment with INF-γ	PAM +MT with INF-a		28	IV,90mg,Q4W	14m	14m
			Healthy controls		45			
Berenson 2000(22)	RCT	MM/BC METAST with at least 1 osteolytic lesion without prior biphosphonate treatment	ZOL 0.4mg		68	IV,0.4mg,Q4W,5' infusion	10m	10m
			ZOL 2mg		72	IV,2mg,Q4W,5' infusion		
			ZOL 4mg		67	IV,4mg,Q4W,5' infusion		
			PAM		73	IV,90mg,Q4W, 2h infusion		
McCloskey 2001(66)	RCT - MRC VI MYELOMA STUDY	MM	CLOD		264	PO,1600mg,daily		Until death or up to 8y
			PLC		272			
Terpos 2000(70)	RCT	MM newly diagnosed without prior biphosphonate treatment 3 months before entry	PAM+CHEMO		32	IV,90mg,Q4W	14m	14m
			CHEMO		30			
Abildgaard 1998(50)	RCT - CROSS SECTIONAL SUBSTUDY OF DANISH-SWEDISH PAMIDRONATE STUDY	MM pts who had treatment for at least 12m	PAMIDR 300MG		10	PO,300mg,daily	24.5m(12-48)	
			PLC		6		28.5m(12-45)	
Berenson 1998(44)	RCT	MM stage III+ a lytic lesion and no prior biphosphonate treatment 2m before entry	PAM	1st line chemo 2nd line chemo	196	IV,90mg,Q4W	17.5m	28.2m
			PLC	1st line chemo 2nd line chemo	181		17.8m	28.7m
McCloskey 1997(65)	RCT- VIth MRC MULTIPLE MYELOMA TRIAL	MM NEW without previous cytotoxic treatment	CLOD 1600MG		264	PO,1600mg,daily		2.8y (max 7.5) 926p-y
			PLC		272			921p-y
Brincker 1998(46)	RCT - SWEDISH-DANISH PAMIDRONATE STUDY GROUP	MM newly diagnosed no previous chemo	PAM		152	PO,300mg,daily	544d(4-1701)	2-5y
			PLC		148		551d(2-1659)	
Elomaa 1996(67)	RCT - SUBGROUP FINNISH STUDY GROUP	MM NEW and no prior biphosphonate treatment	CLODR		126	PO,2.4g,daily	2y	
			PLC		119			

Study ID	**Study Design**	**Population**	**Intervention/Comparator**	Study subarms	**No of Patients**	**Route,dose,frequency**	**Treatment Duration** Median (Range)	**Follow up** Median (Range)
Berenson 1996(43)	RCT - MYELOMA AREDIA STUDY GROUP	MM stage III,at least 1 osteolytic lesion and no prior biphosphonate treatment 2m before entry	PAM 90MG	1st line chemo 2nd line chemo	196	IV,90mg,Q4W	9cycles	17m
			PLC	1st line chemo 2nd line chemo	181			
Heim 1995(53)	RCT	MM stage I-III, no prior cytotoxic treatment 3m before entry and no prior biphosphonate treatment	CLOD+CHEMO	P1 P2 P3	77	PO,1600mg,daily	P1 319-430d P2 163-252d P3 pts treated at least once	1y
			CHEMO		80		P1 321-435d P2 159-248d P3 pts treated at least once	
Laakso 1994(54)	RCT - SUBGROUP FINNISH STUDY GROUP	MM NEW and no prior biphosphonate treatment-Subgroup of pts with osteolytic lesions during f/u	CLOD		108	PO,2.4g,daily	24m	24m
			PLC		96			
Riccardi 1994(55)	RCT - MM87 PROTOCOL	MM stage I-III	CLOD		193(138)	IM,100mg/d for 10d, Q4-6W	ALL THROUGH SURVIVAL	42m
						IM,300mg/3times on alternate days,Q4-6W		
						IM,600mg/once,Q4W		
			None		148(93)			64m
Clemens 1993(56)	RCT - INTERIM ANALYSIS OF TUBIGEN CENTRE	MM-no cytotoxic treatment 3m prior to entry and no biphosphonate treatment 1m prior to entry	CLOD+CHEMO		14	PO,1600mg,daily	At least 1y	19.6m
			CHEMO only		12			16.5m
Lahtinen 1992(57)	RCT - FINNISH STUDY GROUP	MM newly diagnosed, untreated and no	CLOD		168	PO,2.4g,daily	24m	24m
			PLC		168			

Study ID	Study Design	Population	Intervention/Comparator	Study subarms	No of Patients	Route,dose,frequency	Treatment Duration Median (Range)	Follow up Median (Range)
		prior biphosphonate treatment						
Belch 1991(69)	RCT	MM newly diagnosed with no prior cytotoxic treatment	ETID		92	PO,5mg/kg,daily		3.7y
			PLC		74			
Delmas 1982(58)	RCT	MM with no more than 10 courses of previous chemotherapy	CLOD		7	PO,1600mg,daily	6-18m	18m
			PLC		6			
Siris 1980(59)	CLINICAL TRIAL CROSSOVER DESIGN	MM advanced	CLOD		10	PO,3200mg,daily,	16w (8w CLOD followed by 8w PLC)	16w
			PLC		Same 10			

DENOS:denosumab;ZOL:zoledronic acid;CLOD:clodronate;ETI:etidronate;IBA:ibandronate;PAM:pamidronate;PLC:placebo;OBS:observation;MT:maintenance treatment;MM:multiple myeloma;CHEMO:chemotherapy;RCT:randomized controlled trial;d:days;w:weeks;m:months;y:years;p-y:person-years;p-m:person-months;p-d:person-days;SC:subcutaneous;PO:per os;IV:intravenous;ASCT:autologous stem cell transplantation;CVAD:cyclophosphamide-vincristine-doxorubicine;CTD:cyclophosphamide-thalidomide-dexamethasone;MP:melphalan-prednisolone;THAl:thalidomide;Q4W:every 4 weeks;Q12W:every 12 weeks;mg:miligrams;kg:kilograms;P1:population 1;P2:population 2;P3:population 3;BC:breast cancer;PC:prostate cancer;INF-a:interferon-a;METAST:metastatic;pts:patients

Figure 2 ROB-2 Weighted summary plot of the risk of bias assessment of the included RCTs for skeletal related events outcome

	Randomization process	Deviations from intended interventions	Mising outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Assignment to intervention (the 'intention-to-treat' effect)						
Total number of study = 27						
Low risk	37	77,8	88,9	88,9	40,7	11,1
Some concerns	51,9	14,8	0	3,7	11,1	33,3
High risk	11,1	7,4	11,1	7,4	48,1	55,6
Adhering to intervention (the 'per-protocol' effect)						
Total number of study = 0						
Low risk						
Some concerns						
High risk						

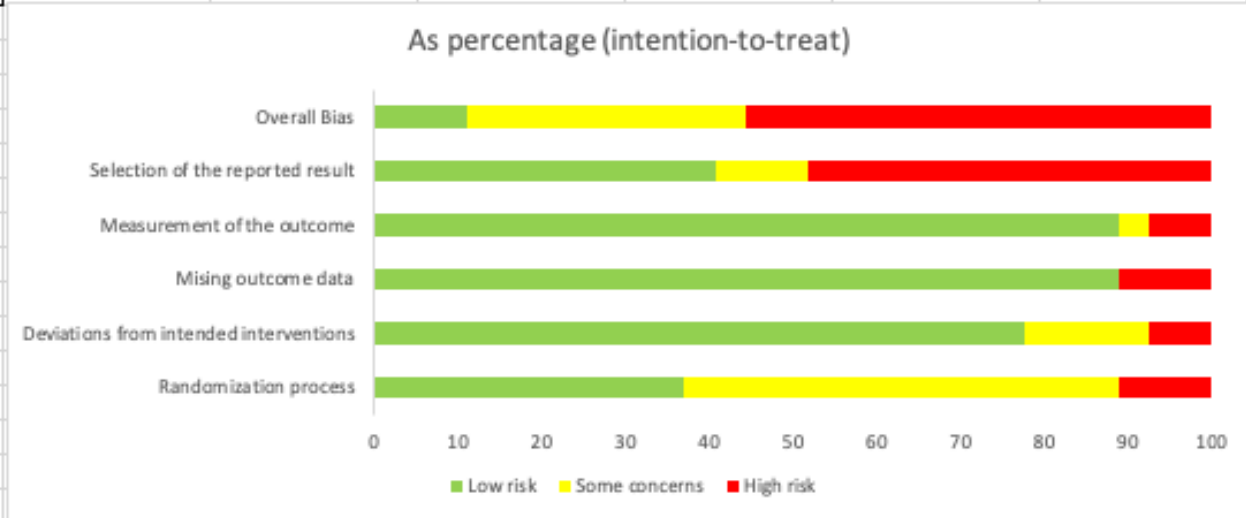
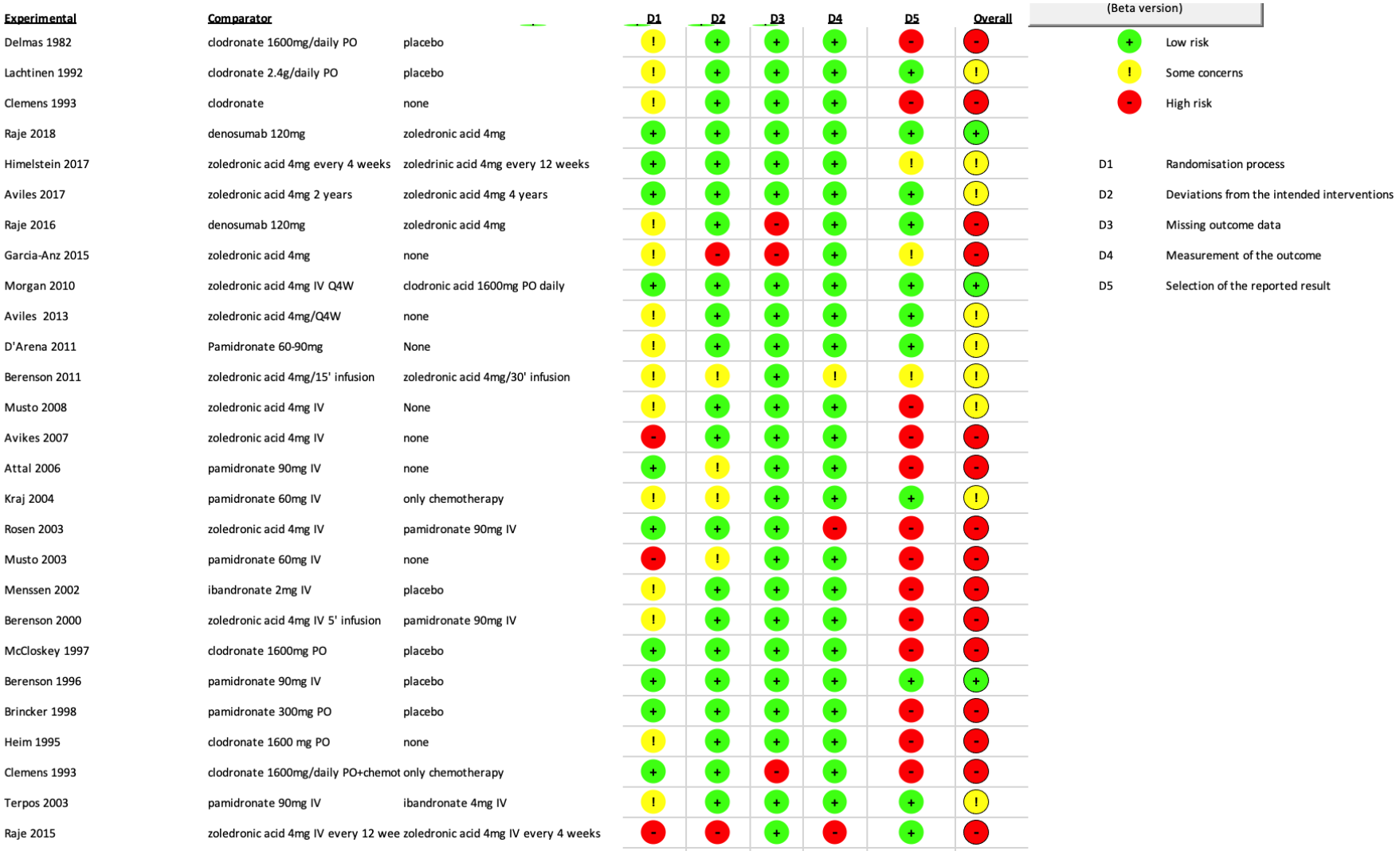


Figure 3 ROB-2 Results of RCTs for skeletal related events outcome



Experimental	Comparator		D1	D2	D3	D4	D5	Overall
Delmas 1982	clodronate 1600mg/daily PO	placebo	!	+	+	+	-	-
Lachtinen 1992	clodronate 2.4g/daily PO	placebo	!	+	+	+	+	!
Clemens 1993	clodronate	none	!	+	+	+	-	-
Raje 2018	denosumab 120mg	zoledronic acid 4mg	+	+	+	+	+	+
Himelstein 2017	zoledronic acid 4mg every 4 weeks	zoledrinic acid 4mg every 12 weeks	+	+	+	+	!	!
Aviles 2017	zoledronic acid 4mg 2 years	zoledronic acid 4mg 4 years	+	+	+	+	+	!
Raje 2016	denosumab 120mg	zoledronic acid 4mg	!	+	-	+	+	-
Garcia-Anz 2015	zoledronic acid 4mg	none	!	-	-	+	!	-
Morgan 2010	zoledronic acid 4mg IV Q4W	clodronic acid 1600mg PO daily	+	+	+	+	+	+
Aviles 2013	zoledronic acid 4mg/Q4W	none	!	+	+	+	+	!
D'Arena 2011	Pamidronate 60-90mg	None	!	+	+	+	+	!
Berenson 2011	zoledronic acid 4mg/15' infusion	zoledronic acid 4mg/30' infusion	!	!	+	!	!	!
Musto 2008	zoledronic acid 4mg IV	None	!	+	+	+	-	!
Avikes 2007	zoledronic acid 4mg IV	none	-	+	+	+	-	-
Attal 2006	pamidronate 90mg IV	none	+	!	+	+	-	-
Kraj 2004	pamidronate 60mg IV	only chemotherapy	!	!	+	+	+	!
Rosen 2003	zoledronic acid 4mg IV	pamidronate 90mg IV	+	+	+	-	-	-
Musto 2003	pamidronate 60mg IV	none	-	!	+	+	-	-
Menssen 2002	ibandronate 2mg IV	placebo	!	+	+	+	-	-
Berenson 2000	zoledronic acid 4mg IV 5' infusion	pamidronate 90mg IV	!	+	+	+	-	-
McCloskey 1997	clodronate 1600mg PO	placebo	+	+	+	+	-	-
Berenson 1996	pamidronate 90mg IV	placebo	+	+	+	+	+	+
Brincker 1998	pamidronate 300mg PO	placebo	+	+	+	+	-	-
Heim 1995	clodronate 1600 mg PO	none	!	+	+	+	-	-
Clemens 1993	clodronate 1600mg/daily PO+chemot	only chemotherapy	+	+	-	+	-	-
Terpos 2003	pamidronate 90mg IV	ibandronate 4mg IV	!	+	+	+	+	!
Raje 2015	zoledronic acid 4mg IV every 12 wee	zoledronic acid 4mg IV every 4 weeks	-	-	+	-	+	-

Table 3 Outcomes regarding OS,PFS & SRE

Study ID	Intervention/Comparator	Study subarms	OS Median or ratio (95% CI)	PFS Median or ratio (95% CI)	DP Median or ratio (95% CI)	TTSRE or TTDP Median or ratio (95% CI)	SRE Median or ratio (95% CI)
Terpos 2021	DENOS+PLC (IV)	ASCT-intent. ASCT-no intent		46.1m HR 0.65 (0.49,0.85) 30.4m HR 1.01(0.79,1.30)			
		Pt Age <70y		HR 0.74(0.59,0.94) for denosumab			
		Pt age>70y		HR 0.97(0.71,1.33)			
	ZOL+ PLC (SC)	ASCT-intent ASCT-no intent		35.7m 34.7m			
		Pt Age <70y Pt age>70y					
Huang 2020	DENOS+PLC (IV)			29.7m HR 0.71(0.39,1.28)			38.8% HR 0.77(0.48,1.26)
	ZOL+ PLC (SC)			30.2m			50.5%
Raje 2018	DENOS+PLC (IV)		HR 0.90(0.70–1.16)	46.1m HR 0.82(0.68,0.99)		22.8m HR 0.98(0.85,1.14) p=0.10(non inferiority) Post-hoc analysis at 15m HR 0·66(0·44,0·98) p=0·039	
	ZOL+ PLC (SC)			35.4m		24m	
Himelstein 2017	ZOL						29.5% (all types malignancies) For MM patients only OR 0.06 [99.9% CI, −0.12 to 0.24]
	ZOL						28.6% (all types of malignancies)
Aviles 2017	ZOL		68%(60%,76%) p=0.88	75%(64%,82%) p=0.7			21% p<0.001

Study ID	Intervention/Comparator	Study subarms	OS Median or ratio (95% CI)	PFS Median or ratio (95% CI)	DP Median or ratio (95% CI)	TTSRE or TTDP Median or ratio (95% CI)	SRE Median or ratio (95% CI)
	ZOL(control)		68%(62%,75 %)	72%(62%,78%)			43%
Raje 2016	DENOS					HR 1.03(0.68,1.57)	HR 1.21(0.86,1.71)
	ZOL						
Raje 2016	ZOL						5.8% 1st y 4.9% 2nd y
Garcia-Sanz 2015	ZOL monotherapy		73% p=0.161 but marginally significant in those who had bone lesions at entry 61% vs 32% p=0.064		67% p=0.05		6% p<0.001 projected 4-year risk
	None		0,46		83%		40%
Witzig 2013	ZOL+THAL			86% 1st y p=0.0048 HR 1.98(1.1,3.6)		2.4y(1.4,3.6)	
	ZOL			55% 1st y		1.2y (0.7,2.5) HR 2.05(1.1,3.8)	
Aviles 2013	ZOL		67%(60.1,72%) p<0.001	66%(60,73%) p<0.001			14%(22pts)
	None		48%(43.9,55.4%)	52%(46,57%)			24%(38pts)
Morgan 2013	ZOL intensive pathway	CVAD vs CTD	52m HR 0.86(0.77, 0.97)	19m HR0.89(90.80,0.98)			
	ZOL non-intensive pathway	MP vs CTDa					
	CLOD intensive pathway	CVAD vs CTD	Overall 46m	Overall 18m			
	CLOD non intensive pathway	MP vs CTDa					
Larocca 2013	ZOL intensive pathway		PR HR 0.53(0.32,0.86) VGPR HR 0.91(0.54,1.54) CR HR 0.98(0.70,1.36)				VGPR HR 0.74(0.52,1.05) CR HR 1.05[(0.82,1.35)
	CLOD intensive pathway						
Vadhan-Raj 2012	DENOS+(IV) PLC					19m	31.4%

Study ID	Intervention/Comparator	Study subarms	OS Median or ratio (95% CI)	PFS Median or ratio (95% CI)	DP Median or ratio (95% CI)	TTSRE or TTDP Median or ratio (95% CI)	SRE Median or ratio (95% CI)
						HR 0.83 (0.71,0.97)[1]	
	ZOL+(SC) PLC					14.4m	36.3%
Morgan 2012	ZOL intensive pathway	CVAD vs CTD		HR 0.90 p=0.173			27.9% HR 0.76 p=0.017
	ZOL non-intensive pathway	MP vs CTDa	HR 0.83 p=0.049	HR 0.87 p=0.065			Overall ZOL vs CLOD p=0.0102
	CLOD intensive pathway	CVAD vs CTD					36.3%
	CLOD non intensive pathway	MP vs CTDa					
Morgan 2011	ZOL intensive pathway	CVAD vs CTD					28% p=0.003 Overall ZOL vs CLOD HR 0.72 (0.62–0.84)
	ZOL non-intensive pathway	MP vs CTDa					26% p=0.008
	CLOD intensive pathway	CVAD vs CTD					36%
	CLOD non intensive pathway	MP vs CTDa					34%
Berenson 2011	ZOL 15' INFUSION						19%
	ZOL 30' INFUSION						21%
Henry 2011	DENOS+IV PLC		HR 0.95 (0.83,1.08)		HR 1.00 (0.89,1.12)	HR 0.84(0.71,0.98) p=0.0007 (non inferior but not superior when adjusted for multiplicity)	
	ZOL+SC PLC						
D'Arena 2011	PAM		NS	46m p=NS	62.9% p=NS		39.% p=0.009
	NT			48m	62.5%		72.7%
Morgan 2010	ZOL intensive pathway	CVAD vs CTD	p=0.74 Overall HR 0.84 (0.74–0.96) Overall 50m	overall HR 0.88(0.80,0.98]) 12% improvement 19·5 m(IQR 18·0–21·0) HR 0.90 ([0.78,1.05) (intensive)			27% p=0.0004

Study ID	Intervention/Comparator	Study subarms	OS Median or ratio (95% CI)	PFS Median or ratio (95% CI)	DP Median or ratio (95% CI)	TTSRE or TTDP Median or ratio (95% CI)	SRE Median or ratio (95% CI)
	ZOL non-intensive pathway	MP vs CTDa	p=0.13	HR 0.87(0.74,1.01)			
	CLOD intensive pathway	CVAD vs CTD	Overall 44.5m	17.5m(IQR 16.5-19.5)			35%
	CLOD non intensive pathway	MP vs CTDa					
Musto 2008	ZOL			At 5y 42% OR, 1.03(0.55,1.92)		67m p=0.83	55.5% OR 2.90(1.04,8.06)
	OBSERV			42.7%		59m	78.3%
Aviles 2007	ZOL +CHEMO		80% p<0.01	20% p<0.01			21% p=Signif
	CHEMO		0,46	0,48			47%
Attal 2006	NO MAINTENANCE		77% (at 4y) p=0.7 between A/B p<0.03 between B/C p=0.04 between C/A+B	38% (at 3y) p=0.7 between A/B p<0.01 between B/C p=0.03 between C/A+B			24% p=0.4
	PAM		74% (at 4y)	39% (at 3y)			21%
	PAM+THAL		87% (at 4y)	51% (at 3y)			18%
Kraj 2004	PAMID 60MG+CHEMO		21m p=0.78			13m	52% p=0.42
	CHEMO		20m			7m	0,56
Terpos 2003	IBA +CHEMO				90.4% no progr		
	PAM+CHEMO				86.9% no progre		
Rosen 2003	ZOL 4mg					380d p=0.538	RR 0.932 p=0.53 ZOL 4mg vs PAM
	ZOL 8mg/4mg						49% RR 0.854(0.728,1.001) (overall population) vs PAM
	PAM					286d	
Musto 2003	PAM				25% p=NS	16m p=NS	40% (the progressed pts) p<0.001
	NT				26.8%	17.4m	81.8%
Menssen 2002	IBA		33.1m (MD)			438d(MD)	No sign differ
	PLC		28.2m(MD) p=NS			462d(MD)	
Terpos 2001	PAM +MAINT TR with INF-a				Not observed		Not observed
	Healthy controls						

Study ID	Intervention/Comparator	Study subarms	OS Median or ratio (95% CI)	PFS Median or ratio (95% CI)	DP Median or ratio (95% CI)	TTSRE or TTDP Median or ratio (95% CI)	SRE Median or ratio (95% CI)
Berenson 2001	ZOL 0.4mg					167d p<0.05 in favour of PAM	46% p<0.05 in favour of PAM
	ZOL 2mg					175d	35%
	ZOL 4mg					231d	33%
	PAM					254d ND with ZOL 2/4mg	30% ND with ZOL 2/4mg
McCloskey 2001	CLOD		34m(28, 40) 30% at 5y 13% at 8y p=NS median survival for pts without vertebral # 59m((43,71) p=0.004 Good prognosis group 8y survival 38%				
	PLC		36m((31,42) 29% at 5y 9% at 8y median survival for pts without vertebral # 37m((31-52) Good prognosis group 8y survival 10%				
Berenson 1998	PAM	1st line chemo 2nd line chemo	26m p=0.37 21m				38% p=0.015 at 21c vertebral # 16% p=0.005 at 21c
	PLC	1st line chemo 2nd line chemo	24m 14m			Shorter than PAM p=0.016	51% at 21c vertebral # 27% p=0.005 at 21c
McCloskey 1997	CLOD 1600MG		2.9y((2.4,3.4) p=0.74 pts with vertebral # at entry p=NS pts without vertebral # at entry better survival p=0.05 OR 0.64				non-vertebral # 20 # p<0.025 vertebr# 80 # p=0.012
	PLC		2.8y(2.5,3.5)				non-vertebr# 36 # vertebral # 146 #

Study ID	Intervention/Comparator	Study subarms	OS Median or ratio (95% CI)	PFS Median or ratio (95% CI)	DP Median or ratio (95% CI)	TTSRE or TTDP Median or ratio (95% CI)	SRE Median or ratio (95% CI)
Brincker 1998	PAM					440d p=0.33	Mean events/year(SD)0.69(1.02) p=0.27
	PLC					414d	Mean events/year(SD)0.97(1.44)
Berenson 1996	PAM 90MG	1st line chemo (133) 2nd line chemo (63)	28m (MD) survival at 17m did not differ sign			Lower in PLC p<0.001	Total SRE lower for PAM in both stratum(1,2) p=0.04/p=0.004 Pathologic # reduction for PAM in stratum 1 p=0.01 but not stratum 2
	PLC	1st line chemo (114) 2nd line chemo (67)	23m (MD)				
Heim 1995	CLOD+CHEMO				Bone progression sites P1 p=0.09 less for CLOD P2 p=0.06 less for CLOD		
	CHEMO				0,53		
Laakso 1994	CLOD				Pts without bone lesions at baseline 2.6% bone progression Pts with bone lesions at baseline 17.4 % bone progression CLOD prevented progression OR=0.39(0.18-0.86).		
	PLC				2-fold bone disease progression vs CLOD Pts without bone lesions at baseline 11.1% bone progression Pts with bone lesions at baseline 31.7 % bone progression		
Riccardi 1994	CLOD		Overall for the planned group 35.1m		47.1% p=NS	15.3m) p=NS	34.8% p<0.02

Study ID	Intervention/Comparator	Study subarms	OS Median or ratio (95% CI)	PFS Median or ratio (95% CI)	DP Median or ratio (95% CI)	TTSRE or TTDP Median or ratio (95% CI)	SRE Median or ratio (95% CI)
			p<0.02 Sign increased OS for the pts who took CLOD 46.1m p<0.009				
	None		31.8m (subset of pts)35.9m		52.2%	11.2m	50.5%
Clemens 1993	CLOD+CHEMO					14.2m(4.5,30)	At 12m 11pts Osteolytic lesions 7 Pathol fractures 12
	CHEMO only					8.5m(4,17)	At 12m 12pts Osteolytic lesions 18 p=signif Pathologic fractures 23
Lahtinen 1992	CLOD		54deaths				Osteolytic lesions 12% p=0.026 Progr of vertebral & non vertebral # similar in both groups
	PLC		68deaths				Osteolytic lesions 24%
Belch 1991	ETID		p=0.02 in favour of PLC	Bone PFS no sign diff			Max change in Vertebral Index p=0.07 Pathologic franc 22% p=NS
	PLC						Pathologic frac 28%
Delmas 1982	CLOD						At 12m no events & 3pts at 18m
	PLC						3 of 6pts at 6m had lytic lesions
Siris 1980	CLOD						5/7pts with significant chemical effects reported lessening of symptoms when underCLOD 3 of them did not report the same when PLC
	PLC (crossover)						

DENOS:denosumab;ZOL:zoledronic acid;CLOD:clodronate;ETI:etidronate;IBA:ibandronate;PAM:pamidronate;PLC:placebo;OBS:observation;MT:maintenance treatment;MM:multiple myeloma;CHEMO:chemotherapy;m:months;y:years; SC:subcutaneous;IV:intravenous;ASCT:autologous stem cell transplantation;CVAD:cyclophosphamide-vincristine-

Study ID	Intervention/Comparator	Study subarms	OS Median or ratio (95% CI)	PFS Median or ratio (95% CI)	DP Median or ratio (95% CI)	TTSRE or TTDP Median or ratio (95% CI)	SRE Median or ratio (95% CI)
doxorubicine;CTD:cyclophosphamide-thalidomide-dexamethasone;MP:melphalan-prednisolone;THAl:thalidomide;P1:population 1;P2:population 2;P3:population 3; INF-a:interferon-a;METAST:metastatic;pts:patients;#:fracture NS: not significant; SD: standard deviation; HR: hazard ratio; OR: odds ratio p:p-value 5% level of significance							

Table 4 Outcomes regarding Bone pain, ONJ & RT

Study ID	Intervention/Comparator	Study subarms	Bone Pain	ONJ	Renal Toxicity
Huang 2020	DENOS+PLC (IV)			6.9%	4.9%
	ZOL+ PLC (SC)			5.4%	0,13
Raje 2018	DENOS+PLC (IV)		23%	4%	10%
	ZOL+ PLC (SC)		21%	3%	17%
Himelstein 2017	ZOL		p=0.96 mean worst pain p=0.38 mean least pain	2%	1.2%
	ZOL			1%	0.5%
Aviles 2017	ZOL			0%	0
	ZOL(control)			0%	0
Raje 2016	ZOL			3.3%	3.3%
Garcia-Sanz 2015	ZOL monotherapy		3pts GRADE I-II bone pain	2%	2%
	None		4 pts GRADE I-II bone pain	0%	4%
Jackson 2014	ZOL	Intensive pathway		3.7% p<0.001	5.2%
		Non-intensive			
	CLOD	Intensive pathway		0.5%	5.8%
		Non-intensive			
Aviles 2013	ZOL			0%	No events
	None			0%	
Vadhan-Raj 2012	DENOS+(IV) PLC		Worst pain 15% 2-point risk reduction moderate/severe 9% 2-point risk reduction mild pain 19% 2-point risk reduction		NM
	ZOL+(SC) PLC				
Berenson 2011	ZOL 15' INFUSION		12%	3 pts	5%
	ZOL 30' INFUSION		13%	7 pts	1%
Henry 2011	DENOS+IV PLC			1.1% p=1	8.3% (11.3% in patients with CrCl<60ml/min)
	ZOL+SC PLC			1.3%	10.9% (21.6% in patients with CrCl<60ml/min)
D'Arena 2011	PAM				10.7% p=NSD
	Simple OBS				10.9%
Morgan 2010	ZOL intensive pathway	CVAD vs CTD		4% p<0.0001	5% p=0.7
	ZOL non-intensive pathway	MP vs CTDa		3%	7% p=0.78
	CLOD intensive pathway	CVAD vs CTD		<1%	6%
	CLOD non intensive pathway	MP vs CTDa		<1% p=0.0009	6%

Study ID	Intervention/Comparator	Study subarms	Bone Pain	ONJ	Renal Toxicity
	PAM			8pts	15 pts excluded because of SCr rise
Musto 2008	ZOL			1pt	22.2% p=NSD
	OBS			0	16.2%
Attal 2006	NO MAINTENANCE				1% p=NSD
	PAM			1pt	1%
	PAM+THAL			1pt	2%
Kraj 2004	PAMID 60MG+CHEMO		Reduced P<0.05 After 9th month NSD		NM
	CHEMO				
Vogel 2004	ZOL		Significant pain reduction in at least 4 of the 6 visits	0 cases	Increase SCr 7.8%- treat discount 3.1%
Rosen 2003	ZOL 4mg				0.4% No SD vs PAM
	ZOL 8mg/4mg				2.7% RR 2.187 *P* < 0.001 vs PAM
	PAM				1.9%
Martin 2002	PAM		1pt		NM
Menssen 2002	IBA	46% completed the study	Significant reduction (p=0.047) in pts with osteolytic lesions Overall NSD		No events
	PLC				
Berenson 2001	ZOL 0.4mg		51% decrease in pain score		1 pt
	ZOL 2mg		48%		1 pt
	ZOL 4mg		67%		1 pt
	PAM		50%		2 pts
Terpos 2000	PAM+CHEMO		Reduction p<0.01		No events
	CHEMO		No change		
Berenson 1998	PAM	1st line chemo 2nd line chemo	61% p<0.05		No events
	PLC	1st line chemo 2nd line chemo	71%		
McCloskey 1997	CLOD 1600MG		10.9% had back pain at 24m p<0.05		NM
	PLC		19.9% at 24m		
Brincker 1998	PAM		Mean events/year(SD) 0.58(0.97) p=0.04		No events
	PLC		Mean events/year(SD) 0.80(1.15)		
Heim 1995	CLOD+CHEMO		80-90% of pts reduced pain from 3rd month to end vs PLC		No events
	CHEMO		NSD		
Clemens 1993	CLOD+CHEMO		Improved signif in CLOD during the whole period		No toxicity
	CHEMO only				

Study ID	Intervention/Comparator	Study subarms	Bone Pain	ONJ	Renal Toxicity
Lahtinen 1992	CLOD		53.6% no pain at 24m p=NSD		No events
	PLC		44.6% no pain at 24m		
Belch 1991	ETID		NSD		NM
	PLC				
Delmas 1982	CLOD		Decrease p=0.025 at 6m At 12m 56% mean pain reduction p=0.05		NM
	PLC		Increase at 6m		

DENOS:denosumab;ZOL:zoledronic acid;CLOD:clodronate;ETI:etidronate;IBA:ibandronate;PAM:pamidronate;PLC:placebo;OBS:observation;MT:maintenance treatment;MM:multiple myeloma;CHEMO:chemotherapy;m:months;y:years; SC:subcutaneous;IV:intravenous;ASCT:autologous stem cell transplantation;CVAD:cyclophosphamide-vincristine-doxorubicine;CTD:cyclophosphamide-thalidomide-dexamethasone;MP:melphalan-prednisolone;THAl:thalidomide;P1:population 1;P2:population 2;P3:population 3; INF-a:interferon-a;METAST:metastatic;pts:patients; SCr: serum creatinine; CrCl: creatinine clearance; NM: not mentioned
NSD: no significant difference; RR: relative risk (95% confidence interval)
p:p-value 5% level of significance

APPENDIX

Table 1. Search strategy per database

Database	**Search string**
Pubmed-Medline	Search: multiple myeloma[MeSH Terms]AND biphosphonates[MeSH Terms] Filters: Clinical Trial, Randomized Controlled Trial ("multiple myeloma"[MeSH Terms] AND "diphosphonates"[MeSH Terms]) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter]) Translations multiple myeloma[MeSH Terms]: "multiple myeloma"[MeSH Terms]biphosphonates[MeSH Terms]: "diphosphonates"[MeSH Terms]
Scopus	(TITLE-ABS-KEY (multiple AND myeloma OR plasma AND cell AND myeloma) AND TITLE-ABS-KEY (biphosphonates OR diphosphonates)) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (EXACTKEYWORD , "Human")) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (EXACTKEYWORD , "Diphosphonates") OR LIMIT-TO (EXACTKEYWORD , "Humans") OR LIMIT-TO (EXACTKEYWORD , "Multiple Myeloma") OR LIMIT-TO (EXACTKEYWORD , "Bisphosphonic Acid Derivative") OR LIMIT-TO (EXACTKEYWORD , "Zoledronic Acid"))
Web of Science	(ALL=(multiple myeloma OR plasma cell myeloma)) AND ALL=(biphosphonates OR zoledronic OR pamidronate OR aledronate OR risedronate OR etidronate OR zoledronic acid OR risedronic acid) Refined By:NOT Document Types: Review Articles or Editorial Materials or Letters or Book Chapters Web of Science Categories: Oncology or Hematology or Orthopedics or Immunology
ClinicalTrials.gov	Status: All studies Condition or disease: multiple myeloma Other terms: biphosphonates

Table 2 Studies excluded after full-text screening

Study reference	Reason for exclusion
Canfield RE, Siris ES, Jacobs TP. Dichloromethylene diphosphonate action in hematologic and other malignancies. Bone. 1987;8 Suppl 1:S57-62. PMID: 2961356	No full text available
Thürlimann B, Morant R, Jungi WF, Radziwill A. Pamidronate for pain control in patients with malignant osteolytic bone disease: a prospective dose-effect study. Support Care Cancer. 1994 Jan;2(1):61-5. doi: 10.1007/BF00355241. PMID: 8156259	Phase II study
Slabý J, Spicka I, Hulejová H, Spacek P, Cieslar P, Klener P. Ucinek klodronátu u pacientů s mnohocetným myelomem. Hodnocení specifickými markery osteoresorpce [Effect of clodronate in patients with multiple myeloma. Evaluation of specific markers of bone resorption]. Cas Lek Cesk. 1997 Jan 22;136(2):57-60. Czech. PMID: 9147856	Article in Czeck
Vinholes JJ, Purohit OP, Abbey ME, Eastell R, Coleman RE. Relationships between biochemical and symptomatic response in a double-blind randomised trial of pamidronate for metastatic bone disease. Ann Oncol. 1997 Dec;8(12):1243-50. doi: 10.1023/a:1008238422151. PMID: 9496390	Not relevant population
Koeberle D, Bacchus L, Thuerlimann B, Senn HJ. Pamidronate treatment in patients with malignant osteolytic bone disease and pain: a prospective randomized double-blind trial. Support Care Cancer. 1999 Jan;7(1):21-7. doi: 10.1007/s005200050218. PMID: 9926970.	Not relevant population
Serkies K, Jereczek-Fossa B, Badzio A, Jassem J. Clodronate in the management of bone metastases: a clinical study of 91 patients. Neoplasma. 1999;46(5):317-22. PMID: 10665850.	Not relevant population
Martin Wilhelm, Volker Kunzmann, Susanne Eckstein, Peter Reimer, Florian Weissinger, Thomas Ruediger, Hans-Peter Tony; γδ T cells for immune therapy of patients with lymphoid malignancies. *Blood* 2003; 102 (1): 200–206. doi: https://doi.org/10.1182/blood-2002-12-3665	Phase I/II trial
Berenson JR, Vescio R, Henick K, Nishikubo C, Rettig M, Swift RA, Conde F, Von Teichert JM. A Phase I, open label, dose ranging trial of intravenous bolus zoledronic acid, a novel bisphosphonate, in cancer patients with metastatic bone disease. Cancer. 2001 Jan 1;91(1):144-54. doi: 10.1002/1097-	Phase I
Morris TC, Ranaghan L, Morrison J; Northern Ireland Regional Haematology Group. Phase II trial of clarithromycin and pamidronate therapy in myeloma. Med Oncol. 2001;18(1):79-84. doi: 10.1385/MO:18:1:79. PMID: 11778973.	Phase II
Jagdev SP, Purohit P, Heatley S, Herling C, Coleman RE. Comparison of the effects of intravenous pamidronate and oral clodronate on symptoms and bone resorption in patients with metastatic bone disease. Ann Oncol. 2001 Oct;12(10):1433-8. doi: 10.1023/a:1012506426440. PMID: 11762816.	Not relevant population
Leng Y, Chen SL, Shi HZ. [Effects of pamidronate disodium (Bonin) combined with chemotherapy on bone pain in multiple myeloma]. Space Med Med Eng (Beijing). 2002 Oct;15(5):377-8. Chinese. PMID: 12449148.	Article in Chinese
Ciepłuch H, Baran W, Hellmann A. Combination of pamidronate and thalidomide in the therapy of treatment-resistant multiple myeloma. Med Sci Monit. 2002 Apr;8(4):PI31-6. PMID: 11951079.	Observational study
Wang T, Song ST, Jiang ZF, Bian SG, Wang YJ, Li LQ, Zhu J. [Clinical trial on ibandronate in patients with tumor-associated hypercalcemia]. Zhonghua Zhong Liu Za Zhi. 2004 Dec;26(12):739-41. Chinese. PMID: 15733393.	Article in Chinese
Ma M. [Clinical observation on effect of combined therapy of pamidronati sodium and shenfu injection in treating multiple myeloma caused ostealgia]. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2004 Jan;24(1):67-8. Chinese. PMID: 14976895.	Article in Chinese
James R. Berenson, Ori Yellin, John Crowley, Herbert Duvivier, Youram Nassir, Regina A. Swift; Factors That Determine Overall Survival among Patients (Pts) with Multiple Myeloma (MM) Treated with Zoledronic Acid (ZOL): Lack of Skeletal-Related Events (SREs) and Occurrence of Osteonecrosis of the Jaw (ONJ) Predict	Observational study

Improved Survival.. *Blood* 2007; 110 (11): 4842. doi: https://doi.org/10.1182/blood.V110.11.4842.4842	
Dong M, Feng FY, Zhang Y, Xie GR, Wang YJ, Liu JW, Song ST, Zhou QH, Ren J, Jiao SC, Li J, Wang XW, Chen Q, Wang ZH, Xu N, Feng JF. [Phase III clinical study of zoledronic acid in the treatment of pain induced by bone metastasis from solid tumor or multiple myeloma]. Zhonghua Zhong Liu Za Zhi. 2008 Mar;30(3):215-20. Chinese. PMID: 18756940.	Article in Chinese
Abe Y, Muto M, Nieda M, Nakagawa Y, Nicol A, Kaneko T, Goto S, Yokokawa K, Suzuki K. Clinical and immunological evaluation of zoledronate-activated Vgamma9gammadelta T-cell-based immunotherapy for patients with multiple myeloma. Exp Hematol. 2009 Aug;37(8):956-68. doi: 10.1016/j.exphem.2009.04.008. Epub 2009 May 4. PMID: 19409955.	Observational study
Zhang X, Chang CK, Wu LY, Zhang Z, Zhou LY, Xiao C, Li X. [The affection of bisphosphonates combined with chemotherapy on bone metabolism index in multiple myeloma]. Zhonghua Xue Ye Xue Za Zhi. 2011 Oct;32(10):660-3. Chinese. PMID: 22339822.	Article in Chinese
Zhang X, Chang CK, Zhang Z, Zhao YS, Xiao C, Li X. [Influence of bisphosphonate combined with chemotherapy on bone mineral density of patients with multiple myeloma]. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2012 Oct;20(5):1135-8. Chinese. PMID: 23114134.	Article in Chinese
Teoh G, Chen Y, Kim K, Srivastava A, Pai VR, Yoon SS, Suh C, Kim YK. Lower dose dexamethasone/thalidomide and zoledronic acid every 3 weeks in previously untreated multiple myeloma. Clin Lymphoma Myeloma Leuk. 2012 Apr;12(2):118-26. doi: 10.1016/j.clml.2011.11.002. Epub 2011 Dec 28. PMID: 22206804.	Phase II study
Qu S, Liao LS, Wei TN, Lin Y, Chen BY, Chen WM. [Effect of bortezomib combined with bisphosphonates on bone metabolism index in multiple myeloma]. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2013 Dec;21(6):1482-5. Chinese. doi: 10.7534/j.issn.1009-2137.2013.06.021. PMID: 24370033.	Article in Chinese
Liang B, Yin JJ, Wang ZL, Zhan XR. [Clinical Comparative Study of Two Kind Doses of Bortezomib Combinated with Bisphosphonates for Treating Patients with Multiple Myeloma Ostespathy]. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2016 Jun;24(3):769-72. Chinese. doi: 10.7534/j.issn.1009-2137.2016.03.025. PMID: 27342507.	Article in Chinese
Pyridinium cross-links in multiple myeloma: correlation with clinical parameters and use for monitoring of intravenous clodronate therapy--a pilot study of the German Myeloma Treatment Group (GMTG). Eur J Cancer. 1996 Nov;32A(12):2053-7. doi: 10.1016/s0959-8049(96)00228-6. PMID: 9014744.	No outcome of interest
Smith AG, Soutar RL, Schey S, Andrews CD, Baister ER, Bilbrough C, Connelly M, Joyce A, Child JA. Home care versus hospital care in patients with multiple myeloma treated with pamidronate. Int J Palliat Nurs. 2004 Mar;10(3):144-9. doi: 10.12968/ijpn.2004.10.3.12602. PMID: 15126959.	No outcome of interest
Tosi P, Zamagni E, Cellini C, Parente R, Cangini D, Tacchetti P, Perrone G, Ceccolini M, Boni P, Tura S, Baccarani M, Cavo M. First-line therapy with thalidomide, dexamethasone and zoledronic acid decreases bone resorption markers in patients with multiple myeloma. Eur J Haematol. 2006 May;76(5):399-404. doi: 10.1111/j.0902-4441.2005.t01-1-EJH2520.x. Epub 2006 Feb 15. PMID: 16480429.	No outcome of interest
Spencer A, Roberts A, Kennedy N, Ravera C, Cremers S, Bilic S, Neeman T, Copeman M, Schran H, Lynch K. Renal safety of zoledronic acid with thalidomide in patients with myeloma: a pharmacokinetic and safety sub-study. BMC Clin Pharmacol. 2008 Mar 31;8:2. doi: 10.1186/1472-6904-8-2. PMID: 18377658; PMCID: PMC2330021.	Phase II trial
Gimsing P, Carlson K, Turesson I, Fayers P, Waage A, Vangsted A, Mylin A, Gluud C, Juliusson G, Gregersen H, Hjorth-Hansen H, Nesthus I, Dahl IM, Westin J, Nielsen JL, Knudsen LM, Ahlberg L, Hjorth M, Abildgaard N, Andersen NF, Linder O, Wisløff F. Effect of pamidronate 30 mg versus 90 mg on physical function in patients with newly diagnosed multiple myeloma (Nordic Myeloma Study Group): a double-blind, randomised controlled trial. Lancet Oncol. 2010 Oct;11(10):973-82. doi: 10.1016/S1470-2045(10)70198-4. PMID: 20863761.	Phase II

Royle KL, Gregory WM, Cairns DA, Bell SE, Cook G, Owen RG, Drayson MT, Davies FE, Jackson GH, Morgan GJ, Child JA. Quality of life during and following sequential treatment of previously untreated patients with multiple myeloma: findings of the Medical Research Council Myeloma IX randomised study. Br J Haematol. 2018 Sep;182(6):816-829. doi: 10.1111/bjh.15459. Epub 2018 Jul 9. PMID: 29984830; PMCID: PMC6175065.	No outcome of interest
Jung A, Chantraine A, Donath A, van Ouwenaller C, Turnill D, Mermillod B, Kitler ME. Use of dichloromethylene diphosphonate in metastatic bone disease. N Engl J Med. 1983 Jun 23;308(25):1499-501. doi: 10.1056/NEJM198306233082503. PMID: 6222257.	Not relevant outcome
Thiébaud D, Leyvraz S, von Fliedner V, Perey L, Cornu P, Thiébaud S, Burckhardt P. Treatment of bone metastases from breast cancer and myeloma with pamidronate. Eur J Cancer. 1991;27(1):37-41. doi: 10.1016/0277-5379(91)90056-j. PMID: 1826438.	Not relevant population
Fazzi R, Petrini I, Giuliani N, Morganti R, Carulli G, Dalla Palma B, Notarfranchi L, Galimberti S, Buda G. Phase II Trial of Maintenance Treatment With IL2 and Zoledronate in Multiple Myeloma After Bone Marrow Transplantation: Biological and Clinical Results. Front Immunol. 2021 Feb 3;11:573156. doi: 10.3389/fimmu.2020.573156. PMID: 33613510; PMCID: PMC7890401.	Phase II study
Søe K, Delaissé JM, Jakobsen EH, Hansen CT, Plesner T. Dosing related effects of zoledronic acid on bone markers and creatinine clearance in patients with multiple myeloma and metastatic breast cancer. Acta Oncol. 2014 Apr;53(4):547-56. doi: 10.3109/0284186X.2013.844358. Epub 2013 Oct 28. PMID: 24164102.	Phase II study
Coleman RE, Purohit OP, Black C, Vinholes JJ, Schlosser K, Huss H, Quinn KJ, Kanis J. Double-blind, randomised, placebo-controlled, dose-finding study of oral ibandronate in patients with metastatic bone disease. Ann Oncol. 1999 Mar;10(3):311-6. doi: 10.1023/a:1008386501738. PMID: 10355575.	Phase II study
Daragon A, Humez C, Michot C, Le Loet X, Grosbois B, Pouyol F, Euller-Ziegler L, Azais I, Bernard JF, Menard JF, et al. Treatment of multiple myeloma with etidronate: results of a multicentre double-blind study. Groupe d'Etudes et de Recherches sur le Myélome (GERM). Eur J Med. 1993 Oct-Nov;2(8):449-52. PMID: 8258043.	No full text available
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