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How do skeletal morbidity rate and special toxicities affect 12-week versus 4-week schedule zoledronic acid efficacy? A systematic review and a meta-analysis of randomized trials

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ABSTRACT

Background: Zoledronic Acid is a bisphosphonate used in a 4-week schedule for the treatment of bone metastases. Some randomized trials supported its role also when administered every 12 weeks.
Methods: we performed a systematic review and a meta-analysis in order to evaluate the two different schedules in terms of skeletal morbidity rate (SMR), skeletal related events (SRE) and adverse events (AEs).
Results: our results showed a clinical difference favouring the 12-week schedule in terms of AEs (RR 1.17, 95% CI 1.06–1.29). No signifcant differences were found for SMR (RR 0.97, 95% CI 0.84–1.13) and SRE (RR 1.02, 95% CI 0.89–1.16).
Conclusions: Our findings support in clinical practice the 12-week schedule an alternative to the standard 4-week schedule in advanced breast and prostate cancer, in particular when the clinical comorbidities of the patients suggest a higher risk of renal failure or hypocalcaemia.

1. Introduction

The bone health of patients with cancer is deeply influenced both by the treatments received and the cancer itself (Van Poznak et al., 2011). The endocrine therapy and the chemotherapy can cause an impairment of the bone strength and a consequent enhanced risk of fractures (Coleman et al., 2013a); also, the occurrence of bone metastases is associated to major adverse events that can severely impair the prognosis and the quality of life of the patient (Roodman, 2004). The use of zoledronic acid (ZA), a nitrogen containing bisphosphonate, has been demonstrated to provide benefits in very different clinical settings, including the delay of bone metastases occurrence in patients with localized disease (Coleman et al., 2011), the prevention of endocrine treatment-induced bone loss (Coleman et al., 2013b) and the delay and the reduction of skeletal related events in patients with bone metastatic cancer (Rosen et al., 2001; Theriault et al., 1999). The latter effect is of particular interest as bisphosphonates can exert a direct inhibition of cancer cell proliferation (Santini et al., 2003). Due to available evidence (Coleman et al., 2014), ZA approval was granted in 2012 by the European Medical Agency with the indication of skeletal related events prevention in patients with cancer (Anon, 2019). Although this remarkable success, the use of bisphosphonates is linked to potentially severe adverse events such as hypocalcemia, renal failure and osteonecrosis of the jaw (Body, 2001). In order to overcome this issue, a different schedule for ZA has been proposed; in particular, several studies (Hortobagyi et al., 2017; Himelstein et al., 2017; Amadori et al., 2013) investigated whether changing the frequency of ZA injection from ones every 4 to every 12 weeks could affect the efficacy outcomes

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and the safety profile. After a systematic literature review, here we reported the meta-analysis rusults comparing these two different treatment plans as regards the presence of adverse events (AEs), paying attention to parameters not yet well investigated such us skeletal morbidity rate (SMR).

2. Materials and methods

We have searched for RCTs including data on efficacy and safety of zoledronic acid used for the treatment of at least one site of histological confirmed bone metastasis from solid tumors that compared a 4 weeks versus a 12 weeks schedule. We included in our final analysis randomized controlled phase III trial results and excluded phase II trials, trials not in solid tumor setting, other trials in which data were not available or with small sample size (less than 10 patients for arm). We also excluded observational trials to minimize the risk of bias. Data extraction from the original articles was made by two independent authors (D.S. and A.G.) and conflicts were solved by discussion with a third author (A.R.). Data selection was performed using the most relevant scientific electronic database (Medline, EMBASE and Cochrane) up to April 2019, with no language restriction, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009). In particular, relevant abstracts from the international oncological meeting (ASCO, ESMO, AIOM) were included if they met the inclusion criteria and other unpublished data were searched through the ClinicalTrials.gov site (www.clinicaltrials.gov). Mesh terms and free text were performed for the creation of the search strategy (See supplement appendix 1). Data about AEs, skeletal-related events (SRE), time to first skeletal- related event (tSRE), time to multiple skeletal-related events (tmSRE) and SMR were collected and SRE was considered the primary endpoint of our analysis. AE included osteonecrosis of the jaw (ONJ), renal disorders, hypocalcaemia, serious adverse events (SAE) and the discontinuation rate. SRE included bone radiation, pathological fracture (vertebral and nonvertebral), spinal cord compression, bone surgery and malignant hypercalcaemia. SRE subgroup analysis according to different kind of neoplasm was planned, if data available. SMR considered the mean number of skeletal-related events per year.

A quality analysis of selected trials following the criteria reported in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2011) was performed including: allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; sequence generation; elective outcome reporting; other sources of bias. For each study we defined “Yes” as at low risk of bias and as “No” at high risk of bias. We define also “unclear” if there were insufficient data for a precise judgement. Selective outcome reporting bias risk was also evaluated by two independent reviewers (D.S. and A.G.) and disagreement were solved by a third author (A.R.).

For dichotomous outcomes (SRE, AE and SMR) we used relative risk (RR) as measure of association, extracting event/total exposed ratio data. For time-dependent variable (tSRE and tmSRE) we used hazard ratio (HR) with a 95% of confidence interval (CI) as measure of association, extracting the HR logarithm (logHR) and the standard error logarithm (logSE). Heterogeneity between study was evaluated using Chi-square or I-square tests. In particular, if I-square test was higher than 50% we used the random effect-based model according to Der Simonian and Laird (Borenstein and Rothstein, 2008; Higgins and G.S., 2011). Otherwise, we used a fixed-based model by Mantel-Haenszel. We also evaluated the publication bias risk performing the Egger’s test and the related Funnel plot was included in our analysis. All results were considered as statistically significant if p values were ≤ 0.05. Our meta-analysis was performed using Cochrane RevMan ver. 5.3 statistical software and Comprehensive Meta – Analysis ver. 2.0 statistical software to assess the risk of publication bias (Egger’s Test).

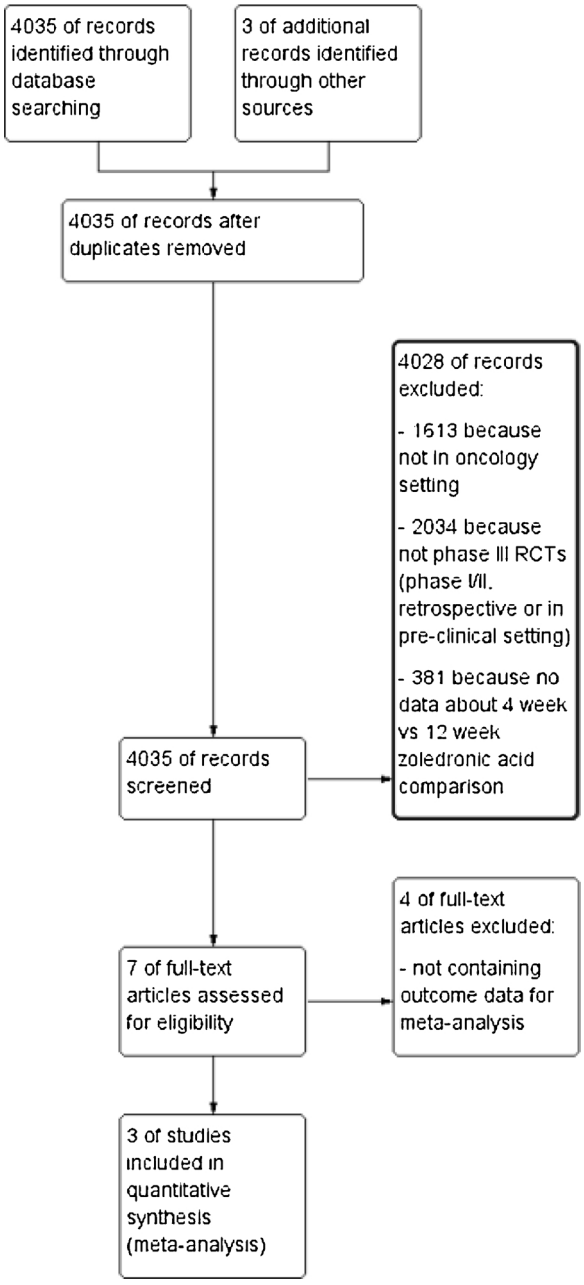

Fig. 1. Study flow diagram.

3. Results

The electronic research identified a total of 4035 records on zoledonic acid, 2422 on its role in cancer-related bone metastases. 2034 articles were excluded because they were retrospective, phase I/II studies or in pre-clinical setting. We also excluded 381 trials because they did not provide data about the schedules comparison (4 weeks versus 12 weeks). A total of 7 trials was assessed for eligibility and 4 trials were excluded because authors did not provide information about the endpoints considered in our analysis (SRE, AE and SMR).

Finally, a total of three studies met all the inclusion/exclusion criteria and were included in the meta–analysis (Fig. 1). All characteristics of included trials are reported in Table 1.

3.1. SRE, SRE subgroup and SRE type

Three RCTs enrolling a total of 2650 patients evaluated SRE and

Table 1
Characteristics of the Trials Included in the Meta – Analysis (tSRE: time to first skeletal event; tmSRE: time to multiple skeletal event).

Study (reference)	Drug (Schedule)	ONJ	Bone Radiation	Pathological fracture (nonvertebral)	Renal Adverse Events (AE)	Hypocalcemia	Serious Adverse Events (SAE)
Hortobagyi, 2017	Zoledronic (12 weeks)	0/202	23/203	18/203	16/202	x	50/203
	Zoledronic (4 weeks)	2/198	29/200	15/200	19/198		51/200
Himelstein, 2017 Breast	Zoledronic (12 weeks)	x	x	x	x	x	x
	Zoledronic (4 weeks)						
Himelstein 2017 prostate	Zoledronic (12 weeks)	x	x	x	x	x	x
	Zoledronic (4 weeks)						
Himelstein 2017 total	Zoledronic (12 weeks)	9/911	163/911	79/911	137/882	298/911	x
	Zoledronic (4 weeks)	18/911	185/911	62/911	174/875	329/911	
Amadori, 2013	Zoledronic (12 weeks)	4/209	22/209	7/209	1/209	x	21/209
	Zoledronic (4 weeks)	3/216	24/216	5/216	2/216		29/216

zoledronic acid schedules (4 weeks versus 12 weeks). Pooled results showed no statistically significant differences between the two different regimens (RR 1.02, 95% CI 0.89–1.16). A subgroup analysis was performed according to different primary tumor (prostate and breast) and even in this case no difference was underlined (RR 1.04 and HR 0.95 respectively, $p > 0.05$) (Fig. 2). As regard SRE type, in our analysis 4 weeks zoledronic acid seems to significantly reduce by 48% the risk of surgery to bone (RR 0.52, 95% CI 0.32 – 0.86) with a positive trend also in reducing spinal cord compression (RR 0.75, $p > 0.05$) and non-vertebral pathological fracture (RR 0.79, $p > 0.05$) events. On the other side 12 weeks schedule could have a positive trend over malignant hypercalcaemia (RR 3.87 $p > 0.05$) and bone radiation events (RR 1.14, $p > 0.05$). Conversely, the two investigated schedules do not interfere w1ith vertebral pathological fracture (RR 1.29, $p > 0.05$) (Fig. 3).

3.2. AEs

AEs represent a critical point in the management of zoledronic acid. Our analysis showed a statistically significant 17% of increased risk for 4 week AEs if compared to the 12 week schedule administration of zoledronic acid (RR 1.17, 95% CI 1.06–1.29). In particular, benefit was registered for all the variables included in the above mentioned AE definition. As a possible consequence, data pooling also showed a clinically relevant and significant discontinuation rate for patients undergone on a 4 week schedule (RR 1.61, 95% CI 1.17–2.21) (Fig. 4).

3.3. tSRE and tmSRE

Our meta-analysis evaluated the role of zoledronic acid in different schedules over time as regards skeletal events and no relevant differences were noted for either tSRE (HR 1.04, $p > 0.05$) and tmSRE (HR 0.99, $p > 0.05$) (Fig. 5).

3.4. SMR

SMR was evaluated in our analysis. Results showed no statistical difference using a different schedule of zoledronic acid (RR 0.97, $p > 0.05$) (Fig. 6)

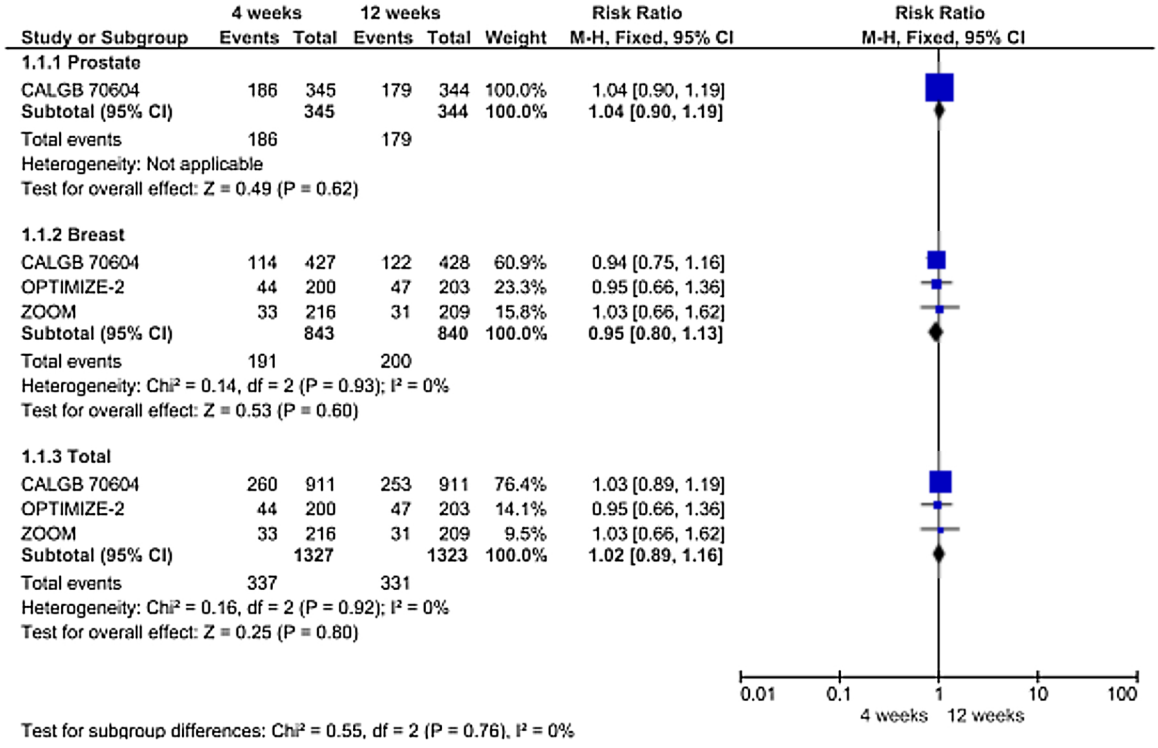

Fig. 2. Forest plot of the zoledronic acid 4-weeks vs 12-weeks schedule comparison for SRE in prostate and breast cancer setting.

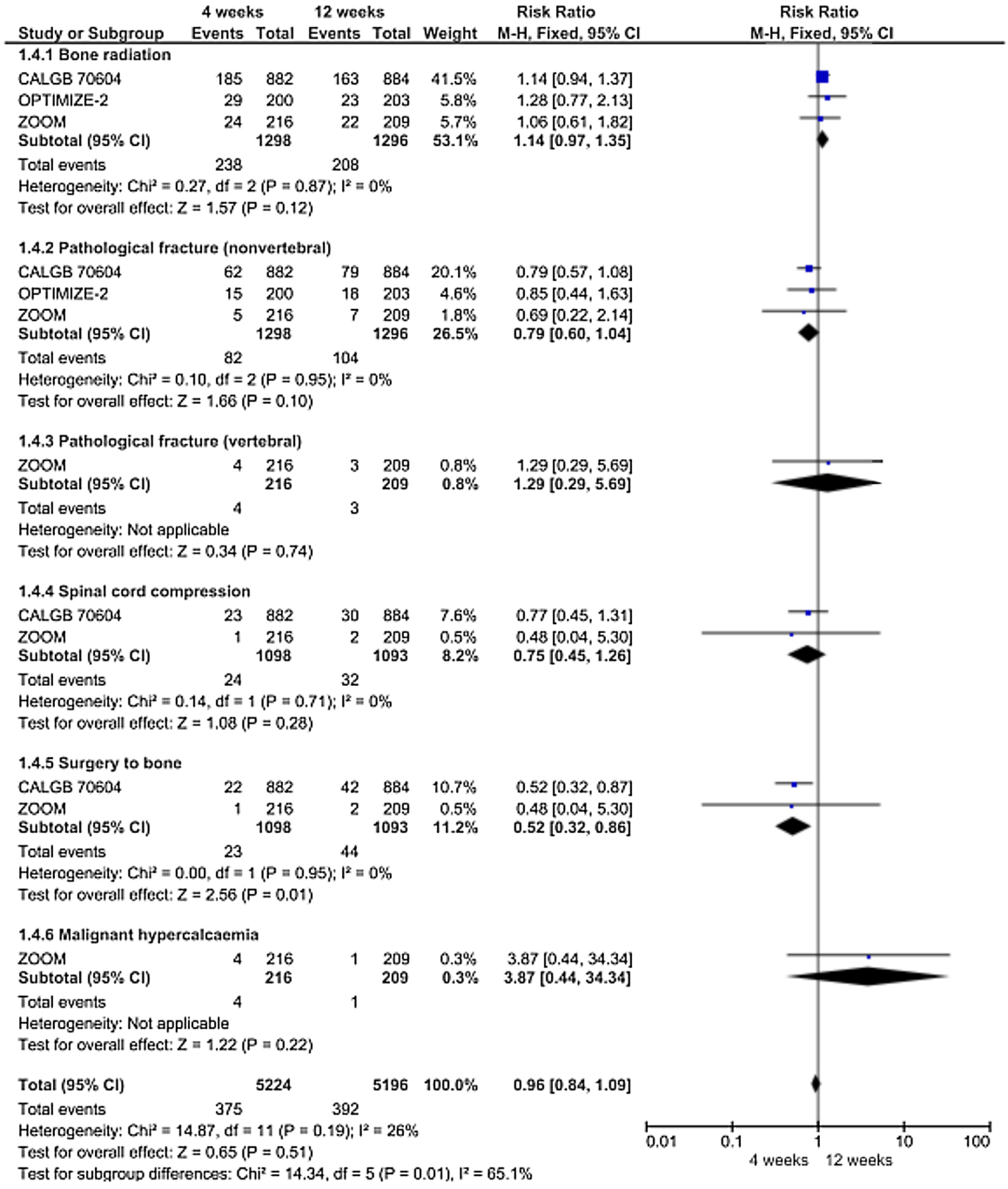

Fig. 3. Forest plot of the zoledronic acid 4-weeks vs 12-weeks schedule comparison according to SRE different type.

3.5. Risk of Bias assessment

Publication bias test is required in a meta-analysis including at least 3 studies. In our analysis, Egger's test was performed showing no significant risk for publication bias ($p > 0.05$) (Funnel plot Fig. 7). The overall quality of included trials was also investigated following the CONSORT checklist statement. We reported an average good quality of all trials. In particular, no severe caution we noted regarding the random sequence generation. Only one trial (ZOOM trial) specified the not masked allocation to treatment of all people involved in the study (participants, personnel and investigators), suggesting an increased risk for a selection bias. Furthermore, in the CALGB 70604 outcome assessment was not blinded resulting in a higher likelihood of detection bias. No significant risk of bias detected for incomplete outcome data and selecting reporting (Figs. 8 and 9).

4. Discussion

The standard schedule of zoledronic in bone metastatic patients with solid tumor consists in one administration every 3–4 weeks from diagnosis of bone metastasis up to a substantial decline in the patient's general performance status. However, this schedule may induce a quite high incidence of renal failure, osteonecrosis of the jaw and hypocalcaemia and no data have been published regarding the safety effects associated with the long-term use of zoledronic acid. For this reason, in the last years there was an increasing interest by oncology community

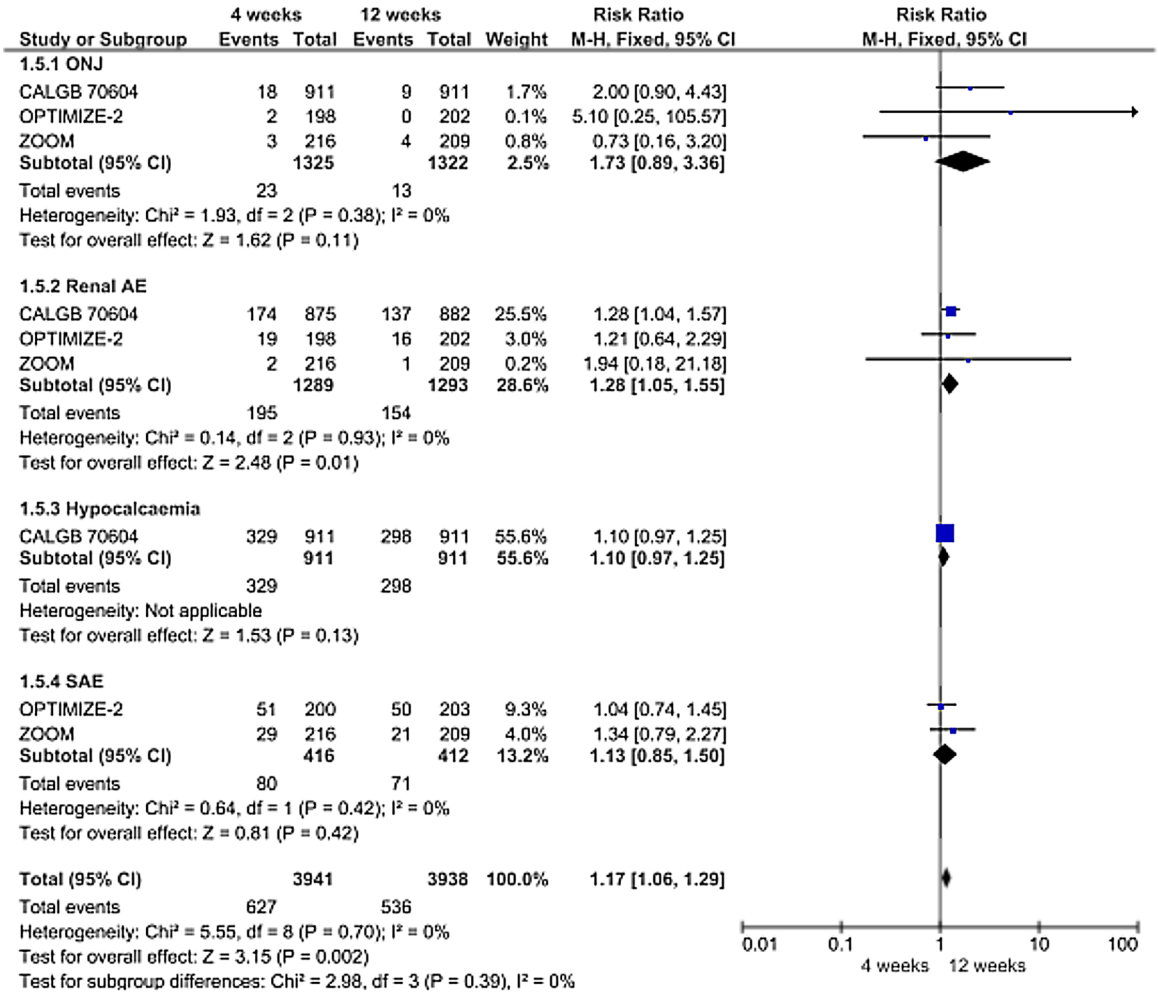

Fig. 4. Forest plot of the zoledronic acid 4-weeks vs 12-weeks schedule comparison for AEs incidence.

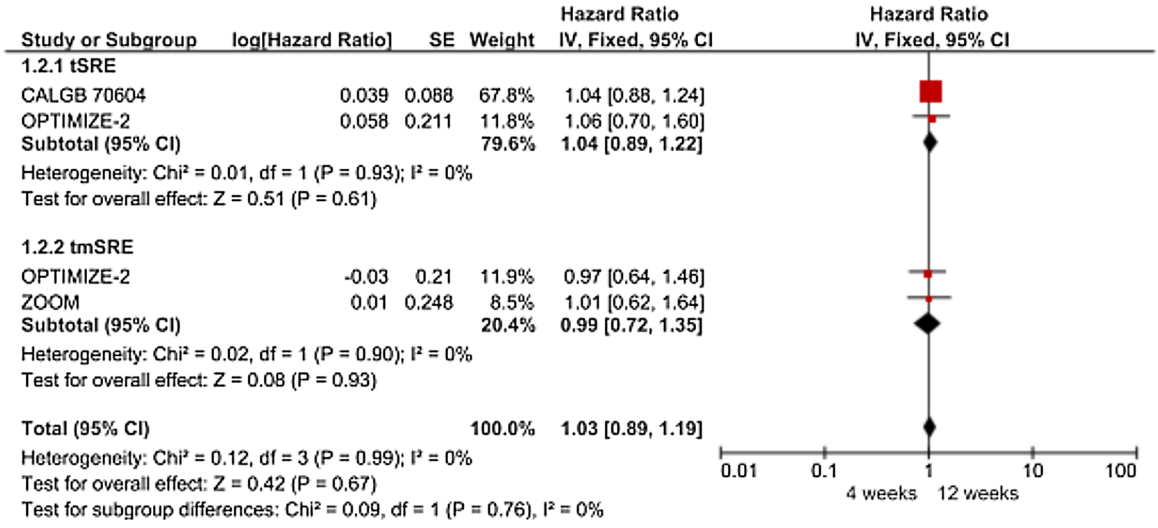

Fig. 5. Forest plot of the zoledronic acid 4-weeks vs 12-weeks schedule comparison for tSRE and tmSRE.

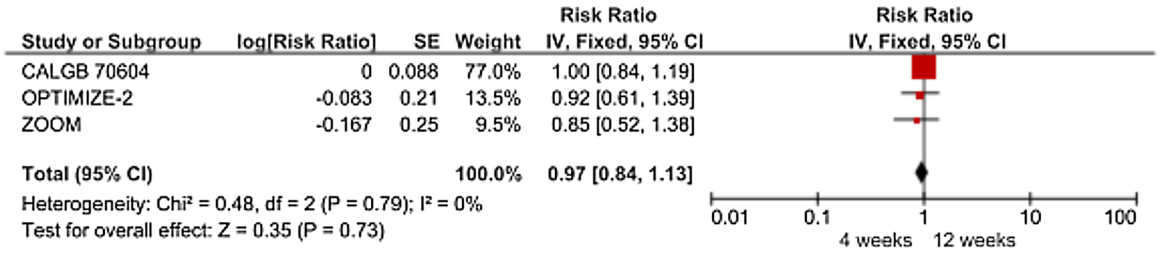

Fig. 6. Forest plot of the zoledronic acid 4-weeks vs 12-weeks schedule comparison for SMR.

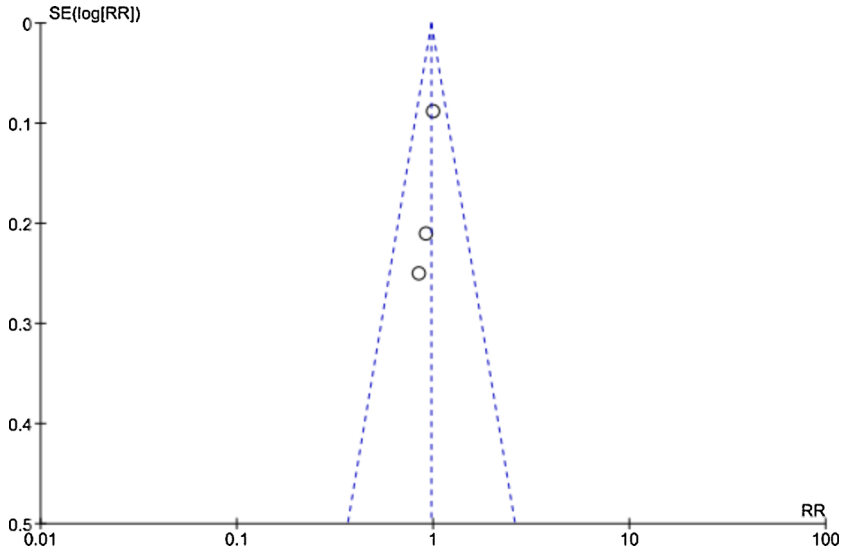

Fig. 7. Funnel plot for publication bias assessment.

to investigate the potential efficacy and safety of alternative, less dose density, schedules of zoledronic acid in different solid tumors (Hortobagyi et al., 2017; Himelstein et al., 2017; Amadori et al., 2013). In our meta-analysis, 12-week dosing intervals of zoledronic acid were comparable to the standard 4-week dosing intervals in reducing the occurrence of SREs, delay the occurrence of SRE and reducing the SMR. Moreover, the 4-week interval demonstrated a clinically relevant and significant discontinuation rate compared with the 12-week interval. Regarding the comparison of safety, in terms of grade 3 or 4 adverse events, osteonecrosis of the jaw and hypocalcaemia were decreased with the 12-week interval; renal dysfunction was significantly reduced (28% reduction of renal impairment). No significant differences reported in terms of SAEs. The comparable effects of the two schedules on SREs were evident for both breast and prostate cancer. The major limit of the present meta-analysis consists in the short median follow-up time of the included RCTs. The long term effects of the 12-week administration on SREs and safety are unknown. Therefore, longer follow-up updates are warranted to investigate if the SRE events will change in the two compared schedules. Despite these evident limits, the present study, as suggested by the previous meta-analysis by Ling Cao (Cao et al., 2017), suggests that compared with the standard 4-week intervals, the administration of zoledronic acid at 12-week intervals do not significantly increase SREs and time to SREs and may reduce the occurrence of jaw osteonecrosis, hypocalcaemia and kidney dysfunction. Additionally, for the first time our results assessed the equivalence of the two different schedules of zoledronic acid in term of SMR. The relevance of this endpoint is supported by previous data suggesting a significant relationship between zoledronic acid administration and bone metastases management on SMR (Poon et al., 2012). Furthermore, we also investigated discontinuation rate reporting a both clinically and statistically significant outcome supporting the 12-week schedule. On the basis of these evidences, we suggest to consider in clinical practice

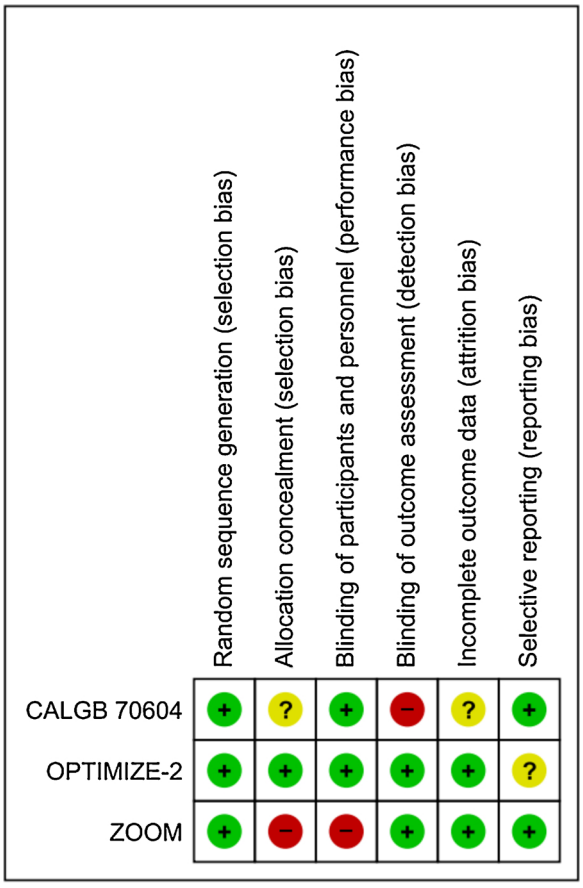

Fig. 8. Risk of bias graph according to review authors' judgments.

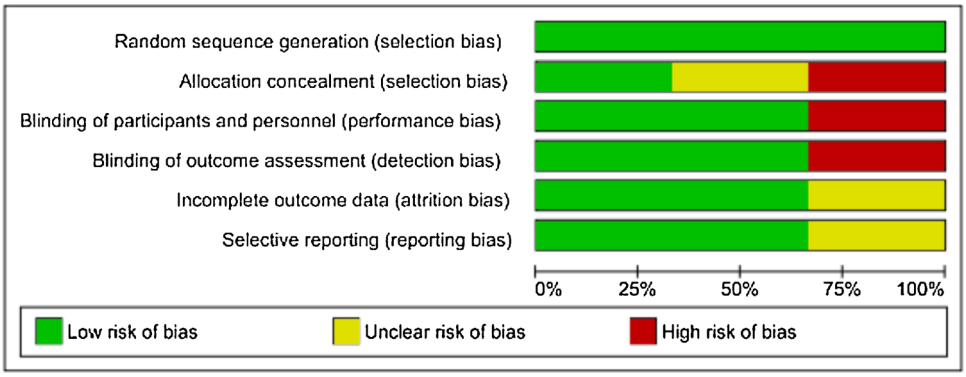

Fig. 9. Risk of bias summary according to review authors' judgments.

the 12-week schedule an alternative to the standard 4-week schedule in advanced breast and prostate cancer, in particular when the clinical comorbidities of the patients suggest a higher risk of renal failure or hypocalcaemia.

Declaration of Competing Interest

All authors have no conflict of interest to disclose.

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CRediT authorship contribution statement

Daniele Santini: Conceptualization, Formal analysis, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing - review & editing. **Antonio Galvano:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Software, Visualization, Writing - original draft, Writing - review & editing. **Francesco Pantano:** Data curation, Formal analysis, Funding acquisition, Visualization. **Lorena Incorvaia:** Data curation, Investigation, Writing - original draft, Writing - review & editing. **Sergio Rizzo:** Data curation, Writing - original draft. **Bruno Vincenzi:** Conceptualization. **Luisa Castellana:** Data curation, Software, Writing - original draft. **Giovanna Giuliana:** Conceptualization, Writing - review & editing. **Fiorella Guadagni:** Investigation, Methodology, Writing - original draft. **Francesca Toia:** Writing - review & editing. **Giuseppe Tonini:** Conceptualization, Investigation, Methodology. **Antonio Russo:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing - review & editing. **Giuseppe Badalamenti:** Data curation, Writing - review & editing. **Viviana Bazan:** Data curation, Investigation, Methodology, Writing - original draft, Writing - review & editing.

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