The Breast 83 (2025) 104565

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast

Denosumab versus zoledronic acid in metastatic breast cancer: A retrospective observational analysis of 24-dose regimens on analgesia and skeletal-related event prevention☆

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ARTICLE INFO

Keywords:
Bone metastases
Bone pain
Denosumab
Zoledronic acid
Skeletal-related events
Breast cancer

ABSTRACT

Background: Based on available data in the literature, current evidence supporting the analgesic role of anti-resorptive drugs is weak. This study compared the efficacy of zoledronic acid (ZA) and denosumab (Dmab) in reducing bone pain and first Skeletal Related Events (SREs) in real world setting.
Methods: A retrospective observational cohort study was conducted in patients with female breast cancer-related bone metastases at the Fondazione IRCCS Istituto Nazionale dei Tumori in Milan, Italy, from January 2008 to January 2023. Patients were included if they had undergone at least 24 consecutive administrations of ZA or Dmab. The primary endpoint was the analgesic effect, evaluated in terms of average pain intensity, analgesic drug use (Word Health Organization analgesic ladder), and daily opioid doses (oral morphine equivalent, OME) assessed at 3, 6, 12, 18, and 24 months, analyzed by Bayesian longitudinal mixed-effects models. Secondary endpoints included first SREs and radiotherapy/surgery incidence.
Results: Among 364 patients (194 ZA, 170 Dmab), Dmab demonstrated a significant analgesic advantage. Dmab group showed an 89 % lower likelihood of increasing one analgesic ladder step, a mean reduction of 0.4 points on the numerical rating scale (95 % CI, −0.7, −0.1), and lower daily OME doses (0.77 mg vs. 6.2 mg for ZA). At 12 and 24 months, ZA and Dmab showed similar cumulative incidences of SREs and radiotherapy/surgery ($p = 0.601$ and $p = 0.923$).
Conclusions: Dmab showed consistent superior effect than ZA in reducing bone pain in metastatic BC, yet both treatments delivered similar protection against SREs and the need for radiotherapy or surgery.

1. Introduction

Bone metastases (BM) represent the main site of distant localization in patients with breast cancer (BC) [1]. They are associated with increased hospitalizations, deterioration of quality of life, and higher mortality rates [2]. Major complications of bone metastases are defined as skeletal-related events (SREs) represented by hypercalcemia, spinal cord compression, and pathological fractures and pain [3,4]. BM and SREs require a multimodal approach, including bone-modifying agents (BMAs). Among BMAs, zoledronic acid (ZA) and denosumab (Dmab), represent the standard of care of BM [5–7]. Randomized controlled trials (RCTs) evaluating the efficacy of antiresorptive agents have shown a

☆ Presentation 1480P: Presented at ESMO Congress 2024 13–Sep 17, 2024 Barcelona—Session Poster session 10 Topics Supportive and Palliative Care.

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https://doi.org/10.1016/j.breast.2025.104565
Received 25 April 2025; Received in revised form 19 August 2025; Accepted 25 August 2025
Available online 27 August 2025

reduction in the incidence of SREs and a delay in the onset of both initial and subsequent SREs in cancer patients [8–14]. Stopeck and al [8]. concluded that Dmab is superior to ZA in delaying or reducing the incidence of SREs.

Patients affected by bone metastases often have pain due to the direct effect of the metastases on the bone or to an SREs [15–17]. A Cochrane review examined the effectiveness of bisphosphonates (BPs) in providing relief of pain due to BM [18]. The authors conclude that, despite evidence suggesting that BMAs provided pain relief, the wide heterogeneity in methods used to assess pain and endpoints precluded a strong recommendation. A panel from the American Society of Clinical Oncology (ASCO) confirmed the weakness of the evidence on this topic [6,7].

RCTs have shown that Dmab delays pain onset or progression [19, 20]. Cleeland and al [19] highlight the effectiveness of Dmab in preventing pain rather than ZA, although both drugs demonstrate similar analgesic efficacy.

A 2017 systematic review represents the most recent update on the topic of pain and BMAs [21]. The evidence supporting an analgesic role for BMAs remains limited because of heterogeneity in pain assessment tools and protocols does not permit a meta-analysis.

This study aims to compare the efficacy of ZA and Dmab in the management of pain and SREs in a cohort of females with bone metastases due to BC treated for at least 24 administrations. This report was conformed to STROBE guidelines [22].

2. Methods

This is a retrospective, single-center, observational study conducted at the Palliative Care Unit of the Fondazione IRCCS Istituto Nazionale dei Tumori in Milan, Italy, from January 2008 to January 2023. Patients were eligible if they were female, at least 18 years old, diagnosed with breast cancer, had at least one bone metastasis, and received at least 24 monthly doses of ZA or Dmab.

The study was approved by the Ethics Committee (number: INT 139/23). Due to the retrospective nature of the study obtaining informed consent was not feasible.

2.1. SRE study definition

As reported in the literature, the need for orthopedic surgery or bone radiotherapy (RT) performed prophylactically before an SRE has often been categorized as an SRE. However, the primary aim of these therapies is to prevent the occurrence of actual skeletal complications and pain worsening. Thus, in this study, RT and orthopedic surgery events were considered as competing factors alongside BMAs in delaying SREs and bone pain. Therefore, our study defined an SRE as follows: pathological fracture (vertebral or non-vertebral), spinal cord compression, and hypercalcemia.

Nevertheless, a sensitivity analysis was conducted in accordance with the conventional composite SRE definition, encompassing RT and orthopedic surgery, to ensure the comparability with prior literature (Supplementary methods).

2.2. Data collection at baseline

The data were obtained from electronic medical records. The following baseline data for ZA or Dmab were collected: age at the start of treatment, primary diagnosis date, histotype, estrogen and progesterone receptor status and ERBB2-positive, history of prior skeletal morbidities, BM diagnosis date and number, previous therapy with others BMAs, ongoing anticancer therapy, baseline Eastern Cooperative Oncology Group performance status (ECOG-PS), week average pain intensity measured through a 0–10 numerical rating scale (NRS) [23] which is part of routine clinical practice at our center, type of analgesia according to the World Health Organization (WHO) (step I non-opioids, step II weak opioids, and step III strong opioids) [24] and opioid consumption doses were expressed as a total daily dose (mg) of oral morphine equivalent (OME) [25].

2.3. Data collection on the treatment period

Patients' follow-up consisted of five subsequent visits, respectively 3,6,12,18, and 24 months after baseline evaluation. The data recorded at each visit were ECOG-PS, ongoing anticancer therapy, bone disease status, visceral disease status, weekly NRS, type of analgesia according to the World Health Organization (WHO) analgesic scale step, opioid consumption, type of SRE and date of the event. The incidence of RT and bone surgery for pain management and fracture prevention or treatment was also recorded.

2.4. Outcomes

The primary outcomes were the analgesic effect of ZA and Dmab on bone pain. Pain outcomes included: 1) weekly average pain intensity measured with NRS, 2) opioid consumption taken during the observational period, and 3) type of analgesic according to the WHO scale. Secondary outcomes were the effect of ZA and Dmab on the onset of the first on-study SRE and the need for RT and/or orthopedic surgery. Safety endpoints included the incidence of adverse events as medical related osteonecrosis of the jaw (MRONJ), and hypocalcemia [26,27] during the treatment period.

2.5. Statistical analysis

Demographic characteristics were summarized using the median, first and third quartile for continuous variables and absolute and relative frequencies for categorical variables.

Three longitudinal Bayesian mixed-effects models were fitted to evaluate the analgesic effects of Dmab and ZA, using three different pain metrics as response variables: the WHO analgesic scale, the NRS, and OME in mg. The three models shared the same covariates and three time-dependent variables: the occurrence of an SRE, type of ongoing oncologic therapy, and RT or surgery. Fixed effects included a categorical time variable with five levels to model changes in the response variable over time, prior BP use, and BMA treatment. Given the ordinal nature of the WHO scale, a Bayesian longitudinal cumulative mixed-effects model was used, where higher Odds Ratios (ORs) corresponded to a greater likelihood of a unit increase in the WHO scale. For OME, a log1p transformation was applied to the response variable in a Gaussian Bayesian mixed-effects (GBME) model to account for zero inflation. A GBME model was also applied to NRS scores. To further quantify the analgesic effects of the two drugs, the conditional effects representing the effects on pain measurements, conditioned on the mean value for numerical covariates and reference level for categorical ones were examined.

Time to first SRE was calculated as the interval between the date of start treatment with ZA or Dmab and the event date. A similar analysis was performed for RT or surgery needs; these local treatments were considered competing events concerning pain control. Observation times, defined as the period from the start of treatment to the last injection date, were censored for patients who did not experience SRE or receive RT or orthopedic surgery within 24 treatment cycles.

Cumulative incidence curves were constructed using the Aalen-Johansen estimator [28] to compare the effect of Dmab and ZA on delaying the onset of the first SRE. Gray's test was used to statistically compare incidence curves. A multivariable Fine-Gray model was built to quantify the effect of Dmab on delaying SREs, and it was also used to assess the relationship between Dmab and the competing events. The following covariates were included as adjustment factors: age, time from metastatic diagnosis and initiation of palliative care, baseline presence of SREs, WHO analgesic scale, NRS, prior BPs use, and baseline

oncologic therapy. For cumulative incidence curves and Fine-Gray models, 95 % confidence intervals (CIs) were reported, whereas 95 % credible intervals were utilized for Bayesian analyses.

To address baseline imbalances and potential residual confounding, inverse-probability-of-treatment weighting (IPTW) and doubly robust (IPTW plus baseline covariate adjustment) sensitivity analyses were performed both for pain outcomes and competing risk ones (Supplementary Methods).

Statistical analyses were performed using R Studio, version 4.3.2.

3. Results

The medical records of 1063 patients with bone metastases from BC who had been administered BMAs were retrospectively reviewed, and 699 patients were excluded (Fig. 1).

Consequently, a total of 364 BC patients treated with BMAs (194 ZA, 170 Dmab) for at least 24 administrations were selected.

Baseline patients' characteristics are reported in Table 1. Good balance between treatment groups was observed for age, ECOG PS, receptors status and histotype, but some statistically significant differences were observed. The time to activation of BMA treatment was longer in the ZA vs Dmab group (4 vs 2.2 months, $p < 0.001$). Prior exposure to oral or intravenous BP was 13.9 % in the ZA and 7.1 % in the Dmab group ($p = 0.004$). The median time between the prior BP last dose and ZA or Dmab start was 17.3 and 1.1 months, respectively ($p = 0.002$). Patients treated with Dmab differed significantly from those treated with ZA in terms of oncologic treatments, 7 % of patients in the ZA group vs 34 % of those in Dmab were treated with hormonal and/or biological therapies.

Study population longitudinal pain characteristics, along with the oncologic therapies, SREs, and RT/Surgery, stratified by treatment, are reported in Table 2.

Fig. 2 shows the trend of the WHO analgesic treatment scale level (percentage; panel A), the NRS (mean; panel B), and the OME (mean mg; panel C) over the observation period in the two treatment groups. Despite the difference in terms of pain intensity observed between the two groups at baseline, as shown in Fig. 2, the analgesic effect of Dmab remains stable over time and was consistently superior to ZA. Thus, the analgesic effect of Dmab appears to be independent from the initial pain levels. Fig. 2B shows the mean NRS score trend in the Dmab and ZA groups. The Dmab group had lower NRS scores compared to the ZA group across each time point. The pain intensity result was linked with a decrease in the percentage at WHO levels 1 and 2. Conversely, the ZA group shows a decline in non-users and an increase in patients requiring weak to moderate-strong opioids (Fig. 2A). Furthermore, the mean OME dosage trend showed consistently lower values in the Dmab group compared to the ZA cohort (Fig. 2C).

The results of the multivariable longitudinal Bayesian models showed that Dmab has a significantly superior analgesic effect compared to ZA (Fig. 3A–F).

Fig. 3A presents the cumulative-logit estimates on the WHO analgesic scale. Dmab vs ZA yields an OR of 0.10 (95 % CI 0.04–0.25), indicating about 90 % lower odds of escalation to a higher WHO step. In absolute terms, model-based probabilities for a representative patient (covariates at the mean) indicate a 93 % probability of remaining at WHO step 0 with Dmab (95 % CI, 86 %–97 %) versus 57 % with ZA (40 %–73 %), and a 1 % probability of requiring WHO≥2 (1 %–3 %) versus 13 % with ZA (6 %–23 %) (Supplementary Table A1; Fig. 3B).

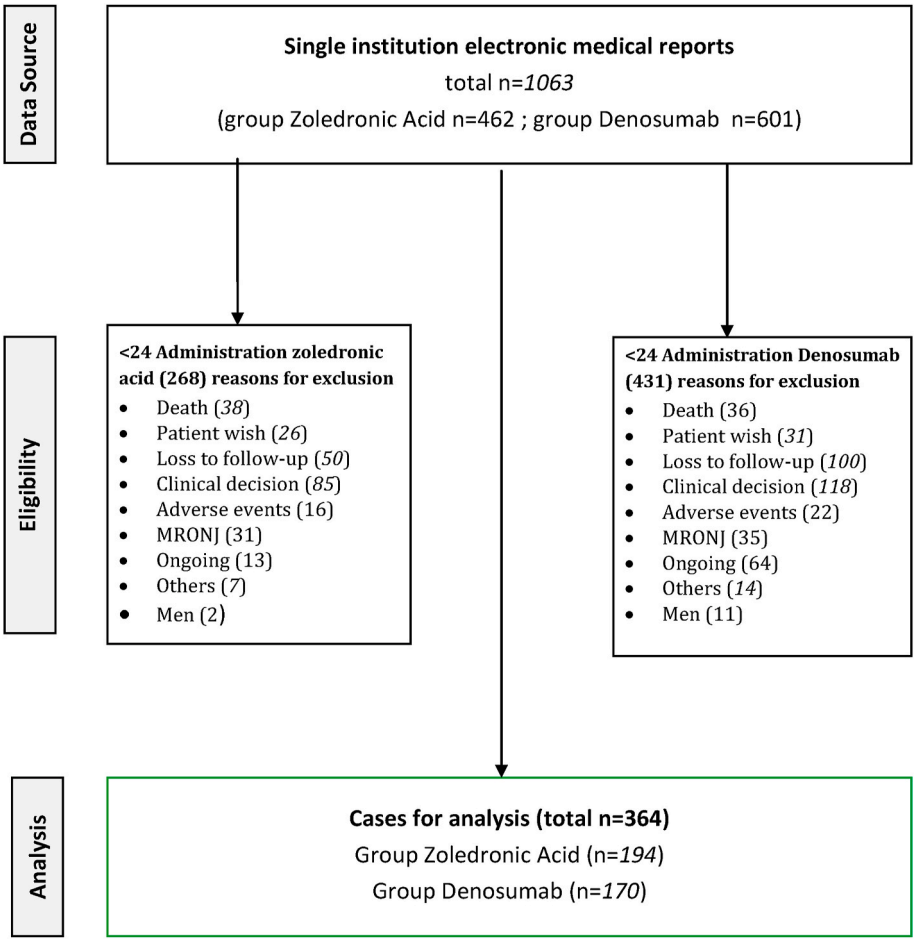

Fig. 1. Flowchart for real-world evidence study.

Table 1
Baseline patients' demographics and characteristics (n = 364).

Characteristic[b]	Zoledronic Acid (n = 194)	Denosumab (n = 170)	p-value[c]
	No (%)	No (%)	
Median Age, years (Q1-Q3)	62.2 (52.7–70.9)	62.2 (50.5–72.0)	0.850
ECOG PS			0.063
0	119.0 (61.3)	118.0 (69.4)	
1	69.0 (35.6)	43.0 (25.3)	
2	6.0 (3.1)	9.0 (5.3)	
Histotype			0.470
Invasive Ductal Carcinoma	144.0 (76.6)	111.0 (71.2)	
Invasive Lobular Carcinoma	29.0 (15.4)	26.0 (16.7)	
Invasive Ductal Carcinoma and Others	1.0 (0.5)	3.0 (1.9)	
Invasive Ductal and Lobular Carcinoma	14.0 (7.4)	16.0 (10.3)	
Unknown	6	14	
Positive HRPR status	164.0 (85.9)	123.0 (82.0)	0.331
Unknown	3	20	
Positive HRER status	177.0 (92.7)	143.0 (93.5)	0.772
Unknown	3	17	
ERBB2-positive	37.0 (20.1)	36.0 (29.8)	0.053
Unknown	10	49	
Median Time from cancer breast diagnosis and first BM, months (Q1-Q3)	77.1 (25.2–148.6)	67.6 (16.3–154.4)	0.760
Median Time from BM diagnosis and start treatment, months (Q1-Q3)	4.0 (2.2–15.1)	2.2 (1.3–4.3)	<0.001
Basal Related Skeletal Event	39.0 (20.1)	47.0 (27.6)	0.091
No of BM to initial diagnoses			0.005
One	164.0 (84.5)	123.0 (72.4)	
Multiple	30.0 (15.5)	47.0 (27.6)	
Previous BPs administration	27.0 (13.9)	12.0 (7.1)	0.035
Median Time from last BPS and new one months (Q1-Q3)	17.3 (9.7–27.9)	1.1 (1.0–2.6)	0.002
Sites of metastasis			0.233
Only bone	120.0 (61.9)	88.0 (51.8)	
Lung	37.0 (19.1)	48.0 (28.2)	
Liver	14.0 (7.2)	15.0 (8.8)	
Brain	20.0 (10.3)	14.0 (8.2)	
Lung, Liver and Brain	3.0 (1.5)	5.0 (2.9)	
Therapy ongoing			<0.001
None	41.0 (21.1)	8.0 (4.7)	
Hormonetherapy	55.0 (28.4)	53.0 (31.2)	
Chemotherapy	37.0 (19.1)	22.0 (12.9)	
Radiotherapy and others[a]	50.0 (25.8)	43.0 (25.3)	
Chemo and/or Biological	4.0 (2.1)	8.0 (4.7)	
Hormone and/or Biological	7.0 (3.6)	34.0 (20.0)	
Basal pain NRS median(Q1-Q3)	2.0 (0.0–4.0)	0.0 (0.0–0.0)	<0.001
WHO scale			0.004
Step 0	121 (62.4)	100 (58.8)	
Step 1	10 (5.2)	28 (16.5)	
Step 2	32 (16.5)	22 (12.9)	
Step 3	31 (16.0)	20 (11.8)	
Total daily dose OME median mg (Q1-Q3)	0.0 (0.0–15.0)	0.0 (0.0–0.0)	0.070

Abbreviations ECOG PS, Eastern Cooperative Oncology Group performance status; HRP, Hormone receptor Progesterone; HRER, Hormone receptor estrogens; BMs, bone metastases; BPs, bisphosphonates; NRS, Numerical Rating Scale; WHO World Health Organization; OME, Oral Morphine Equivalent.

[a] Radiotherapy interrupted from 1 month.

[b] Median (IQR) or Frequency (%).

[c] Wilcoxon rank sum test; Pearson's Chi-squared test; Wilcoxon rank sum exact test; Fisher's exact test.

Fig. 3C provides coefficient estimates for the pain intensity model according to the NRS score. Dmab reduces NRS scores by an average of 0.38 points (95 % CI, −0.65 to −0.11) compared to ZA. Notably, while the NRS ranges from 0 to 10, 80 % of study population values are below NRS 3. Fig. 3D illustrates the conditional effects from the treatment model for pain intensity according to the NRS. Patients receiving Dmab have a mean NRS score of 1.82 (95 % CI, 1.52–2.10), compared to 2.20 (95 % CI, 1.91–2.48) for those in the ZA group (Supplementary Table A1).

Fig. 3E displays the coefficient estimates from the log1p model of opioid dosage in mg OME. Together with Fig. 3F, they show patients receiving Dmab require an average of 0.42 mg (95 % CI, 0.04–1.09) compared to 3.71 mg (95 % CI, 1.69–8.91) in the ZA group (Supplementary Table A1). The OME distribution shows that 80 % of values are below 15 mg, highlighting the difference between 0.42 mg and 3.71 mg in the two groups.

In the overall population, the cumulative incidence (Supplementary Fig. 1) of the first skeletal event is about 28.9 % (95 % CI, 24.2 %–33.7 %). Pathological fractures were the most frequent type of first SRE in ZA (33 %) and in Dmab (28 %) group, followed by grade 1 hypercalcemia (ZA 23 % 2 of them with grade 2 CTCAE and Dmab 24 %). The results of the potentially superior analgesic effect of Dmab were confirmed in the six sensitivity analyses performed (Supplementary Table A2).

The cumulative incidence curves of the first skeletal event and the competitive events (radiotherapy/bone surgery), stratified by anti-resorptive treatment, are reported in Fig. 4. At the 12 months, the cumulative incidence of the first SRE was about 20 % (95 % CI, 14–26 %) and 20 % (14–25 %) for Dmab and ZA respectively, while the cumulative incidence for radiotherapy/bone surgery was about 28 % (21–35 %) and 30 % (24–36 %). At 24 months, the cumulative incidence of the first SRE was about 27 % (20–43 %) and 30 % (23–36 %), while the cumulative incidence for radiotherapy/bone surgery was about 35 % (28–42 %) and 36 % (30–43 %), for denosumab and ZA, respectively. No differences were observed in the occurrence of the first SRE (Gray's test p = 0.601) and incidence of radiotherapy/bone surgery (Gray's test p = 0.923) at both 12 and 24 months between the two cohorts. Differences remained not statistically significant in the multivariable analysis with the Fine-Gray model (Supplementary Tables A3 and A4) for both the first SRE and its competitive event Radiotheraphy/Surgery. Fine-Gray model results were also confirmed in the four sensitivity analyses performed (Supplementary Table A5). Overlaid results were observed when adopting the conventional SRE definition (Supplementary Table A6).

No patients showed symptoms attributable MRONJ [29] and hypocalcemia were generally mild (grade1-2 CTCAE) transient and not associated with clinical sequelae.

4. Discussion

The primary aim of this study was to assess the analgesic effect of Dmab and ZA in this specific population after at least 24 months of treatment.

While clinical trials have demonstrated efficacy of BMAs in delaying the onset of SREs regardless of the presence of symptoms or previous SREs, the overall effect of BMAs on bone pain is a less well-defined topic.

Some RCTs and meta-analyses have demonstrated the efficacy of ZA and Dmab in reducing bone pain when compared to placebo [21]. In particular, Dmab delays the onset of moderate-to-severe pain by 1.8 months compared to ZA, it also reduces the probability of escalating from weak to strong opioids or experiencing a quality of life decline due to pain [16]. However, despite this evidence, there remains a lack of real-world data supporting the analgesic effect of this drug over extended periods of up to 24 months. This is particularly relevant for therapeutic decision-making in common malignancies, such as metastatic BC with or without bone pain [30]. Interestingly, baseline assessment measures show that baseline pain intensity was greater in the ZA group than in the Dmab group (Table 1). This difference may be related to independent changes in the treatment history of the disease (e.g. availability of new biological therapies as early-line therapies for BC in the Dmab cohort) or more prompt access to BMA treatment for the Dmab group.

The findings suggest that Dmab offers superior analgesic effects compared to ZA. Specifically, Dmab was associated with a lower frequency of escalation to higher steps on the WHO scale, a decreased

Table 2
Longitudinal pain assessments, Skeletal Related Events and therapy stratified by treatment.

Characteristic[a]	0 (baseline)	3 months	6 months	12 months	18 months	24 months	p-value[b]
Zoledronic Acid							
Total daily dose OME median mg (Q1-Q3)	0·0 (0·0, 15·0)	0·0 (0·0,15·0)	0·0 (0·0, 15·0)	7·8 (0·0,22·0)	0·0 (0·0, 18·8)	8·0 (0·0, 22·0)	0·004
WHO scale No (%)							<0·001
0	121.0 (62.4)	64.0 (33.0)	58·0 (29·9 %)	59·0 (30·4 %)	62·0 (32·0 %)	56·0 (28·9 %)	
1	10.0 (5.2)	45.0 (23.2)	49.0 (25.3)	37.0 (19.1)	38.0 (19.6)	37.0 (19.1)	
2	32.0 (16.5)	53·0 (27.3)	53.0 (27.3)	57.0 (29.4)	56.0 (28.9)	64.0 (33.0)	
3	31.0 (16.0)	32·0 (16.5)	34.0 (17.5)	41.0 (21.1)	38.0 (19.6)	37.0 (19.1)	
NRS median(Q1-Q3)	2.0 (0.0–4.0)	1.0 (0.0–3.0)	1.0 (0.0–2.0)	1.0 (0.0–3.0)	1.0 (0.0–3.0)	2.0 (0.0–3.0)	<0.001
Oncological Therapy No(%)							<0.001
None	41.0 (21.1)	22.0 (11.3)	20.0 (10.3)	16.0 (8.2)	8.0 (4.1)	14.0 (7.2)	
Chemotherapy	37.0 (19.1)	55.0 (28.4)	48.0 (24.7)	39.0 (20.1)	45.0 (23.2)	41.0 (21.1)	
Hormonetherapy	55.0 (28.4)	98.0 (50.5)	102.0 (52.6)	116.0 (60.0)	117.0 (60.3)	112.0 (57.7)	
Chemo and/or Biological	4.0 (2.1)	12.0 (6.2)	14.0 (7.2)	12.0 (6.2)	12.0 (6.2)	10.0 (5.2)	
Hormone and/or Biological	7.0 (3.6)	7.0 (3.6)	10.0 (5.2)	11.0 (5.7)	12.0 (6.2)	17.0 (8.8)	
SREs No(%)							
Pathologic Fracture	33.0 (17.0)	7.0 (3.6)	15.0 (7.7)	16.0 (8.2)	9.0 (4.6)	17.0 (8.8)	<0.001
SCC	5.0 (2.6)	0.0 (0.0)	2.0 (1.0)	0.0 (0.0)	1.0 (0.5)	1.0 (0.5)	0.062
Hypercalcemia	6·0 (3.1)	3.0 (1.5)	9.0 (4.6)	13.0 (6.7)	13.0 (6.7)	19.0 (9.8)	0.006
Competitive events No(%)							
Radiotherapy	50.0 (25.8)	33.0 (17.0)	20.0 (10.3)	25.0 (12.9)	26.0 (13.4)	19.0 (9.8)	<0.001
Surgery	7·0 (3.6)	2.0 (1.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	<0.001
Denosumab							
Total daily dose OME median mg (Q1-Q3)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.890
WHO scale No (%)							0.670
0	100.0 (58.8)	107.0 (63.0)	115.0 (67.6)	118.0 (69.0)	115.0 (67.6)	114.0 (67.1)	
1	28.0 (16.5)	23.0 (13.5)	18.0 (10.6)	22.0 (12.9)	21.0 (12.4)	21.0 (12.4)	
2	22.0 (12.9)	21.0 (12.4)	16.0 (9.4)	10.0 (5.9)	12.0 (7.1)	14.0 (8.2)	
3	20.0 (11.8)	19.0 (11.2)	21.0 (12.4)	20.0 (11.8)	22.0 (12.9)	21.0 (12.4)	
NRS median(Q1-Q3)	0.0 (0.0–2.0)	0.0 (0.0–2.0)	0.0 (0.0–2.0)	0.0 (0.0–2.0)	0.0 (0.0–2.0)	0.0 (0.0–2.0)	0.523
Oncological Therapy No(%)							<0.001
None	10.0 (5.9)	3.0 (1.8)	6.0 (3.5)	11.0 (6.5)	12.0 (7.1)	13.0 (7.6)	
Chemotherapy	22.0 (12.9)	31.0 (18.2)	28.0 (16.5)	27.0 (15.9)	34.0 (20.0)	48.0 (28.2)	
Hormonetherapy	53.0 (31.2)	66.0 (38.8)	66.0 (38.8)	69.0 (40.6)	68.0 (40.0)	55.0 (32.4)	
Chemo and/or Biological	8.0 (4.7)	14.0 (8.2)	10.0 (5.9)	4.0 (2.4)	7.0 (4.1)	7.0 (4.1)	
Hormone and/or Biological	34.0 (20.0)	56.0 (32.9)	60.0 (35.3)	59.0 (34.7)	49.0 (28.8)	47.0 (27.6)	
SREs No(%)							
Pathologic Fracture	41.0 (24.1)	6.0 (3.5)	10.0 (5.9)	11.0 (6.5)	13.0 (7.6)	13.0 (7.6)	<0.001
SCC	8.0 (4.7)	0.0 (0.0)	1.0 (0.6)	0.0 (0.0)	1.0 (0.6)	2.0 (1.2)	0.001
Hypercalcemia	3.0 (1.8)	3.0 (1.8)	8.0 (4.7)	7.0 (4.1)	11.0 (6.5)	21.0 (12.4)	<0.001
Competitive events No(%)							
Radiotherapy	43.0 (25.3)	36.0 (21.2)	7.0 (4.1)	13.0 (7.6)	18.0 (10.6)	15.0 (8.8)	<0.001
Surgery	9.0 (5.3)	0.0 (0.0)	2.0 (1.2)	0.0 (0.0)	2·0 (1.2)	1.0 (0.6)	<0.001

[a] Median (IQR) or Frequency (%).
[b] Kruskal-Wallis rank sum test; Pearson's Chi-squared test; Fisher's exact test.

likelihood of using higher-level analgesics, and an increased likelihood of not requiring pain medication. This trend is also confirmed by the NRS scale, with values averaging 0.38 points lower than those in the ZA group. Lastly, the mean OME was also lower in the Dmab group, with 0.42 mg compared to 3.71 mg in patients treated with ZA. Despite the differences in NRS intensity and mean OME between the Dmab and ZA groups may appear modest, they should be interpreted in the context of 80 % of patients having an NRS <3 and an average opioid dose <15 mg OME. Thus, the relative impact of Dmab compared to ZA in reducing pain intensity and subsequent opioid needs is significant. From clinical perspective our results show a reduction of patients in need of strong opioids for pain relief (13 % vs 1 % for ZA and Dmab respectively). Future research should investigate whether this effect translates into other tangible benefits for patients, such as improved quality of life or reduced opioid-related toxicity. Moreover, it is also interesting to note that while pain improves following both Dmab and ZA in the first 3 months, overall pain control is better in the Dmab group independently from the difference at baseline (Figs. 2 and 3). This effect can be attributed to the inhibition of the RANK/RANK-L pathway, allowing the drug to block osteoclast activity and reduce the production of cytokines and inflammatory molecules. These molecules impact sensory nerve endings directly or indirectly by promoting inflammation in the surrounding microenvironment [31,32]. These findings could suggest a direct analgesic effect of Dmab, leading to reduced pain intensity and lower opioid requirements. Our data on secondary endpoint indicate no statistically significant difference between ZA and Dmab in delaying or preventing SREs. Fig. 4 shows that the incidences are comparable between the two groups in terms of SRE occurrence as well as the need for RT or orthopedic surgery. These results contrast with evidence from Stopeck et al. [8], where Dmab was superior to ZA in delaying (HR = 0.82) or reducing SREs. However, this may be because our study considered RT and orthopedic surgery as competitive events rather than SREs. Furthermore, studies in the literature were conducted under ideal and controlled conditions.

While ZA and Dmab have shown comparable efficacy in reducing SREs, Dmab appears to have superior analgesic effect and provides certain advantages regarding administration and tolerability.

While our single-center, observational design, and the requirement for ≥24 consecutive doses may limit generalizability, and a randomized clinical trial would be needed to definitely establish the analgesic effect of Dmab, our relatively large sample and broad inclusion/exclusion criteria support a meaningful real-world comparison of the two agents. A further strength of this study is its consideration of the impact of RT and orthopedic surgery on pain, classifying them as competing events rather than SREs. This approach underscores the specific effects of bone-targeting agents on bone pain and SREs.

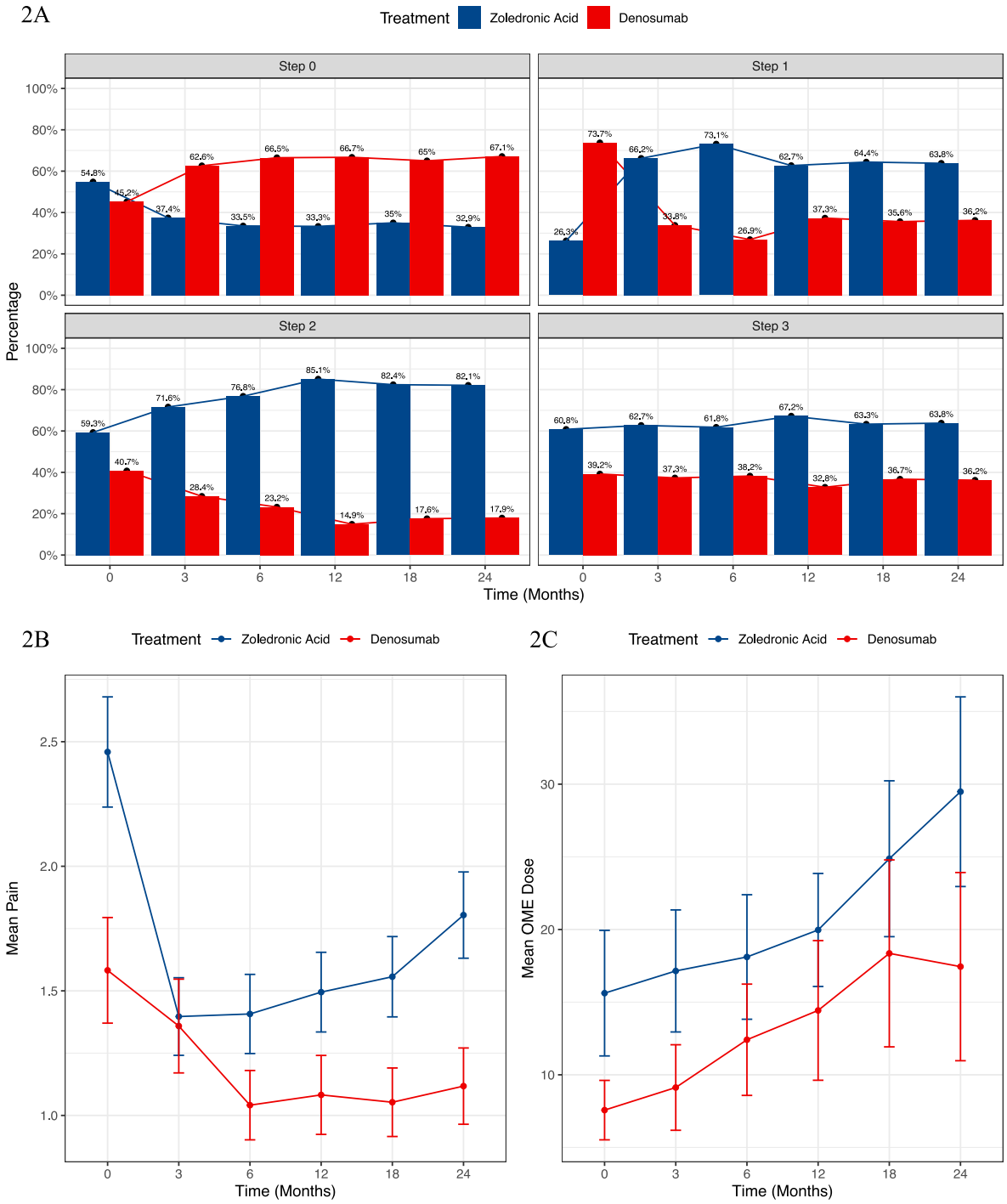

Fig. 2. Trend pattern of pain measurements across 0–24-month period stratified by treatment regimen.
A) changes over time in the WHO analgesic scale (Step 1 non opioid, Step 2 weak opioids, Step 3 Strong opioids, percentage); B) average pain level (NRS value, mean); C) average OME dose (mean in mg). The blue represents the population treated with Zoledronic Acid, and the red represents the population treated with Denosumab. The vertical error bar in B and C represents the 95 %CI. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

5. Conclusion

In BC patients with skeletal metastases, Dmab was associated with consistently better long-term analgesic control than ZA across primary and sensitivity analyses, while prevention of SREs appeared similar between agents. Although the retrospective design cannot exclude residual confounding, these findings suggest Dmab could be a reasonable option for patients offering sustained pain control.

CRediT authorship contribution statement

Giacomo Massa: Writing – original draft, Methodology, Data curation, Conceptualization. **Noemi Simeone:** Writing – original draft, Supervision, Data curation, Conceptualization. **Gabriele Tinè:** Writing –

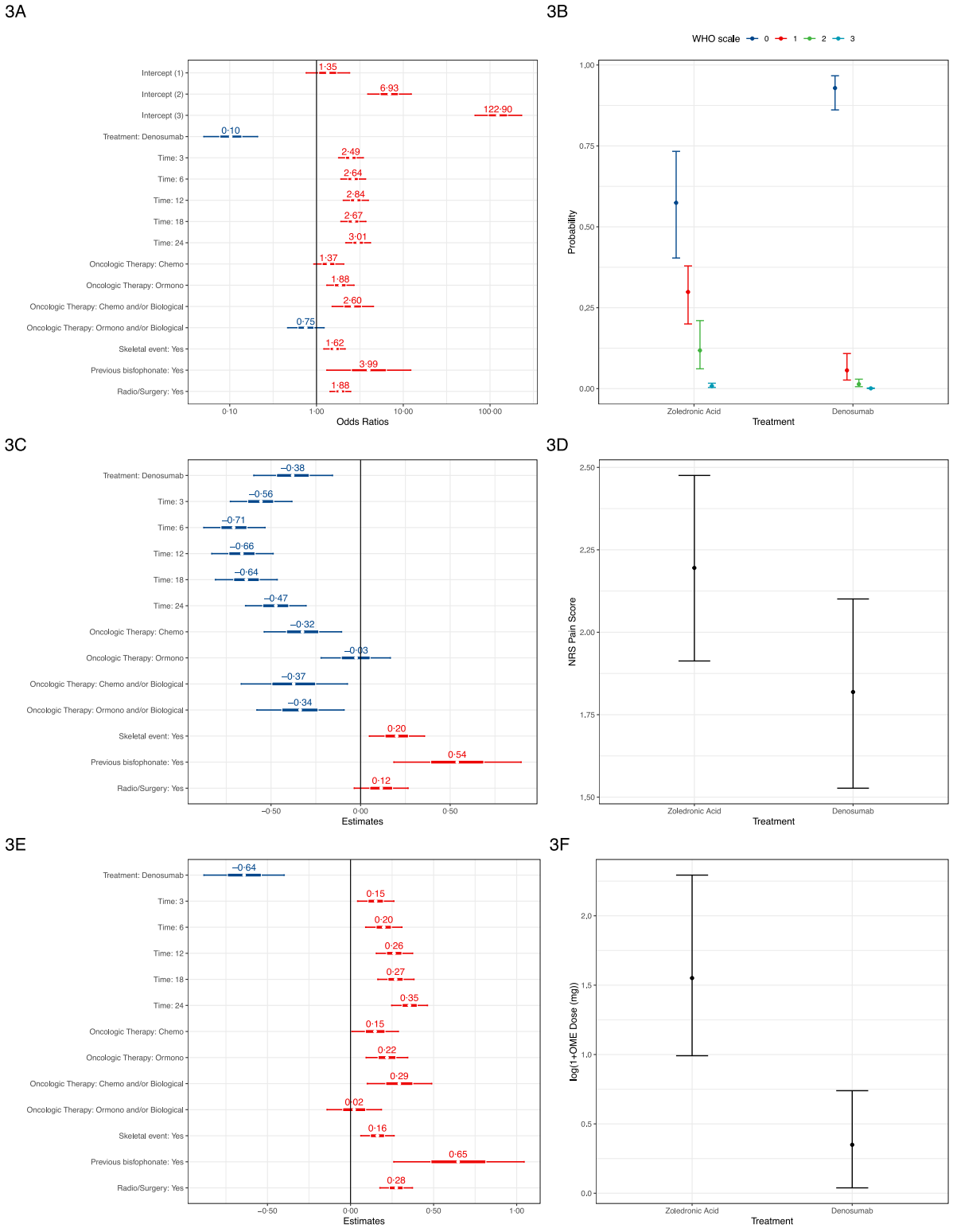

Fig. 3. Results of the Bayesian Mixed Effect Models and marginal effect of treatment regimen on pain
Estimates from the three Bayesian models for each of the pain metrics: (A–B) analgesic use based on the WHO Scale, (C–D) average pain level during the previous week according to NRS, (E–F) average opioid dose in mg OME expressed as log1p. For each pain metric, the figures on the left display the Odds Ratios (WHO analgesic scale) or the coefficient estimates (for the NRS score and opioid dosage in mg OME), while the figures on the right represent the treatment marginal effect.

original draft, Software, Methodology, Formal analysis. **Paola Bracchi:** Validation, Methodology, Data curation. **Rosalba Miceli:** Software, Methodology, Formal analysis, Data curation. **Alessandra Pigni:** Methodology, Data curation. **Silvia Lo Dico:** Validation, Methodology, Data curation. **Luca Zambelli:** Validation, Methodology, Data curation. **Francesca Ricchini:** Validation, Methodology, Data curation. **Giulia Valeria Bianchi:** Validation, Methodology, Data curation. **Augusto Caraceni:** Writing – original draft, Validation, Supervision,

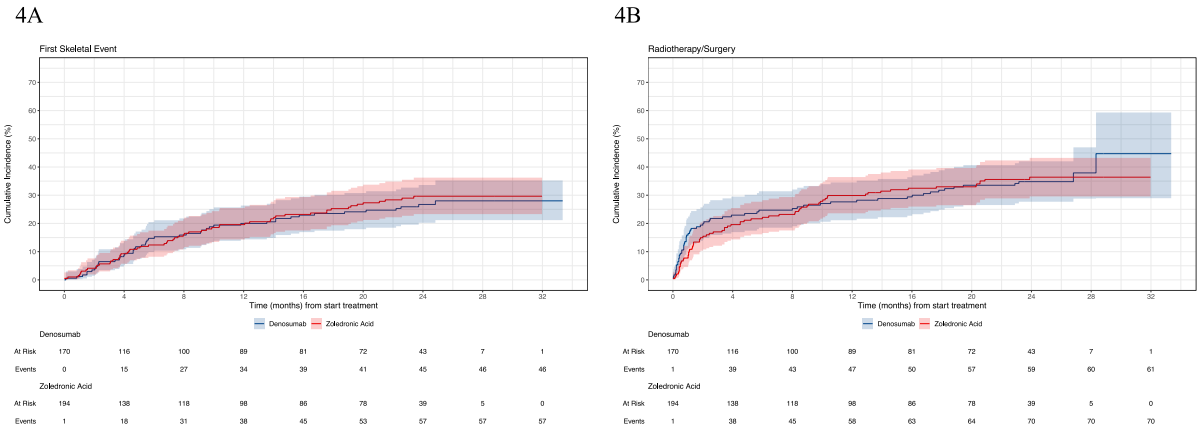

Fig. 4. Cumulative incidence curves of the first skeletal event and the competitive events Cumulative incidence curves of the first SRE (A) and radiotherapy or bone surgery (B), and 95 % CI, stratified for Treatment.

Methodology, Data curation, Conceptualization. **Ernesto Zecca:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Data curation, Conceptualization.

Data sharing

Data supporting this study are not publicly available due to confidentially on the research participants. Please contact the authors Zecca and Tinè. The sample identifiers contained in this paper are not known to anyone outside the research group.

Ethical considerations

The study was conducted in line with the Declaration of Helsinki principles and approved by the Territorial Ethics Committee (Lombardia 4) (INT 139/23).

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Giacomo Massa reports a relationship with Leopharma, Merck that includes: board membership and travel reimbursement.Dr Zecca has received honoraria from Amgen.Prof Caraceni has received honoraria from Angelini, Shionogi, Kyowa Kirin, Molteni, Pfizer/Eli Lilly Italia SPA.Dr Bianchi has received honoraria from Roche, Novartis, Seagen, AstraZeneca/Daiichi Sankyo, Lilly.All remaining authors have declared no conflict of interest.

Acknowledgments

We thank Anna Mazzucchelli, Monica Ullio, Federica Rusconi and Angela DeLeone, nursing staff at the outpatient Palliative Care Clinic of the Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, who actively participated in study execution.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2025.104565.

References

[1] Weilbaecher KN, Guise TA, McCauley LK. Cancer to bone: a fatal attraction. Nat Rev Cancer 2011 Jun;11(6):411–25. https://doi.org/10.1038/nrc3055.
[2] Cetin K, Christiansen CF, Sværke C, Jacobsen JB, Sørensen HT. Survival in patients with breast cancer with bone metastasis: a Danish population-based cohort study on the prognostic impact of initial stage of disease at breast cancer diagnosis and length of the bone metastasis-free interval. BMJ Open 2015 Apr 29;5(4):e007702. https://doi.org/10.1136/bmjopen-2015-007702.
[3] Coleman RE. Skeletal complications of malignancy. Cancer 1997 Oct 15;80(8 Suppl):1588–94. https://doi.org/10.1002/(sici)1097-0142(19971015)80:8+<1588::aid-cncr9>3.3.co;2-z.
[4] Coleman R, Cancer Network. Impact of bone-targeted treatments on skeletal morbidity and survival in breast cancer [cited 2024 Dec 23], https://www.cancernetwork.com/view/impact-bone-targeted-treatments-skeletal-morbidity-and-survival-breast-cancer; 2016.
[5] Vallet S, Smith MR, Raje N. Novel bone-targeted strategies in oncology. Clin Cancer Res 2010 Aug 15;16(16):4084–93. https://doi.org/10.1158/1078-0432.CCR-10-0600.
[6] Van Poznak CH, Temin S, Yee GC, Janjan NA, Barlow WE, Biermann JS, et al., American Society of Clinical Oncology. American Society of Clinical Oncology executive summary of the clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. J Clin Oncol 2011 Mar 20;29(9):1221–7. https://doi.org/10.1200/JCO.2010.32.5209. Epub 2011 Feb 22. Erratum in: J Clin Oncol. 2011 Jun 1;29(16):2293.
[7] Van Poznak C, Somerfield MR, Barlow WE, Biermann JS, Bosserman LD, Clemons MJ, et al. Role of bone-modifying agents in metastatic breast cancer: an American Society of Clinical Oncology-Cancer Care Ontario Focused Guideline update. J Clin Oncol 2017 Dec 10;35(35):3978–86. https://doi.org/10.1200/JCO.2017.75.4614.
[8] Stopeck AT, Lipton A, Body JJ, Steger GG, Tonkin K, de Boer RH, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol 2010 Dec 10;28(35):5132–9. https://doi.org/10.1200/JCO.2010.29.7101.
[9] Martin M, Bell R, Bourgeois H, Brufsky A, Diel I, Eniu A, et al. Bone-related complications and quality of life in advanced breast cancer: results from a randomized phase III trial of denosumab versus zoledronic acid. Clin Cancer Res 2012 Sep 1;18(17):4841–9. https://doi.org/10.1158/1078-0432.CCR-11-3310.
[10] Lipton A, Fizazi K, Stopeck AT, Henry DH, Brown JE, Yardley DA, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. Eur J Cancer 2012 Nov;48(16):3082–92. https://doi.org/10.1016/j.ejca.2012.08.002.
[11] Lipton A, Fizazi K, Stopeck AT, Henry DH, Smith MR, Shore N, et al. Effect of denosumab versus zoledronic acid in preventing skeletal-related events in patients with bone metastases by baseline characteristics. Eur J Cancer 2016 Jan;53:75–83. https://doi.org/10.1016/j.ejca.2015.09.011.
[12] O'Carrigan B, Wong MH, Willson ML, Stockler MR, Pavlakis N, Goodwin A. Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev 2017 Oct 30;10(10):CD003474. https://doi.org/10.1002/14651858.CD003474.pub4.

[13] Menshawy A, Mattar O, Abdulkarim A, Kasem S, Nasreldin N, Menshawy E, et al. Denosumab versus bisphosphonates in patients with advanced cancers-related bone metastasis: systematic review and meta-analysis of randomized controlled trials. Support Care Cancer 2018 Apr;26(4):1029–38. https://doi.org/10.1007/s00520-018-4060-1.
[14] Eisen A, Somerfield MR, Accordino MK, Blanchette PS, Clemons MJ, Dhesy-Thind S, et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: ASCO-OH (CCO) guideline update. J Clin Oncol 2022 Mar 1;40(7):787–800. https://doi.org/10.1200/JCO.21.02647.
[15] Kane CM, Hoskin P, Bennett MI. Cancer induced bone pain. Br Med J 2015 Jan 29;350:h315. https://doi.org/10.1136/bmj.h315.
[16] von Moos R, Body JJ, Egerdie B, Stopeck A, Brown JE, Damyanov D, et al. Pain and health-related quality of life in patients with advanced solid tumours and bone metastases: integrated results from three randomized, double-blind studies of denosumab and zoledronic acid. Support Care Cancer 2013 Dec;21(12):3497–507. https://doi.org/10.1007/s00520-013-1932-2.
[17] Patrick DL, Cleeland CS, von Moos R, Fallowfield L, Wei R, Öhrling K, Qian Y. Pain outcomes in patients with bone metastases from advanced cancer: assessment and management with bone-targeting agents. Support Care Cancer 2015 Apr;23(4):1157–68. https://doi.org/10.1007/s00520-014-2525-4.
[18] Wong RK, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases. Cochrane Database Syst Rev 2002 Apr 22;2002(2):CD002068.
[19] Cleeland CS, Body JJ, Stopeck A, von Moos R, Fallowfield L, Mathias SD, et al. Pain outcomes in patients with advanced breast cancer and bone metastases: results from a randomized, double-blind study of denosumab and zoledronic acid. Cancer 2013 Feb 15;119(4):832–8. https://doi.org/10.1002/cncr.27789.
[20] von Moos R, Body JJ, Egerdie B, Stopeck A, Brown J, Fallowfield L, et al. Pain and analgesic use associated with skeletal-related events in patients with advanced cancer and bone metastases. Support Care Cancer 2016 Mar;24(3):1327–37. https://doi.org/10.1007/s00520-015-2908-1.
[21] Porta-Sales J, Garzón-Rodríguez C, Llorens-Torromé S, Brunelli C, Pigni A, Caraceni A. Evidence on the analgesic role of bisphosphonates and denosumab in the treatment of pain due to bone metastases: a systematic review within the European Association for Palliative Care guidelines project. Palliat Med 2017 Jan;31(1):5–25. https://doi.org/10.1177/0269216316639793.
[22] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. STROBE initiative. The strengthening the reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008 Apr;61(4):344–9. https://doi.org/10.1016/j.jclinepi.2007.11.008.
[23] Nugent SM, Lovejoy TI, Shull S, Dobscha SK, Morasco BJ. Associations of pain numeric rating scale scores collected during usual care with research administered patient reported pain outcomes. Pain Med 2021 Oct 8;22(10):2235–41. https://doi.org/10.1093/pm/pnab110.
[24] Ventafridda V, Tamburini M, Caraceni A, De Conno F, Naldi F. A validation study of the WHO method for cancer pain relief. Cancer 1987 Feb 15;59(4):850–6. https://doi.org/10.1002/1097-0142(19870215)59:4<850::aid-cncr2820590432>3.0.co;2-856.
[25] Caraceni A, Hanks G, Kaasa S, Bennett MI, Brunelli C, Cherny N, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol 2012 Feb;13(2):e58–68. https://doi.org/10.1016/S1470-2045(12)70040-2.
[26] Common terminology criteria for adverse events (CTCAE). 2017.
[27] Toxicity and response criteria of the Eastern Cooperative Oncology Group - PubMed [Internet]. [cited 2025 Jan 7]. Available from: https://pubmed.ncbi.nlm.nih.gov/7165009/.
[28] Aalen OO, Johansen S. An empirical transition matrix for non-homogeneous markov chains based on censored observations. Scand J Stat 1978;5(3):141–50.
[29] Bracchi P, Zecca E, Brunelli C, Miceli R, Tinè G, Maniezzo M, et al. A real-world study on the prevalence and risk factors of medication related osteonecrosis of the jaw in cancer patients with bone metastases treated with Denosumab. Cancer Med 2023 Sep;12(17):18317–26. https://doi.org/10.1002/cam4.6429.
[30] Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. IMMPACT. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005 Jan;113(1–2):9–19. https://doi.org/10.1016/j.pain.2004.09.012.
[31] Walsh MC, Choi Y. Regulation of T cell-associated tissues and T cell activation by RANKL-RANK-OPG. J Bone Miner Metabol 2021 Jan;39(1):54–63. https://doi.org/10.1007/s00774-020-01178-y.
[32] Gómez-Aleza C, Nguyen B, Yoldi G, Ciscar M, Barranco A, Hernández-Jiménez E, et al. Inhibition of RANK signaling in breast cancer induces an anti-tumor immune response orchestrated by CD8+ T cells. Nat Commun 2020 Dec 10;11(1):6335. https://doi.org/10.1038/s41467-020-20138-8.