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**Research Article**

# Administration and cancer-control outcomes of bone-modifying agents in real-world patients with metastatic castration-resistant prostate cancer

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## Abstract

Hormonal agents administered for metastatic castration-resistant prostate cancer (mCRPC) may lead to osteoporosis, skeletal events, reduced quality of life, and even reduced overall survival (OS). Bone-modifying agents may prevent those events but their effect on cancer-control outcomes remains uncertain. Relying on our institutional tertiary-care database, we explored the effect of bone-modifying agents (bisphosphonates such as zoledronic acid and denosumab) on OS and progression-free survival in patients with mCRPC with at least 1 bone metastasis using Kaplan-Meyer estimates and Cox regression models. Of 420 patients with mCRPC, 60% received bone-modifying agents who were younger (68 vs 69 years), with more systemic treatment lines for mCRPC (3 vs 2), and a higher proportion of initial de novo metastatic disease (72% vs 62%, all $p \leq .04$) than patients without bone-modifying agents. In progression-free survival analyses, no significant differences were observed between both groups. In OS analyses, significant median OS differences were observed in favor of patients with bone-modifying agents (58 vs 45 months; hazard ratio [HR]: 0.66), even after multivariable adjustment (HR: 0.37; both $p \leq .01$). In bone-modifying agent–stratified analyses, 57% received denosumab vs 43% bisphosphonates, with a significantly higher rate of Eastern Cooperative Oncology Group status of $\geq$2 in the bisphosphonates group. In progression-free and OS analyses, no significant differences were observed between bisphosphonates and denosumab patients, with numerically better results in progression-free survival analysis for denosumab after adjusting for covariates. The cumulative rate of osteonecrosis of the jaw at any treatment time was 12% in both groups and significantly decreased over time. Real-world data suggest a relatively low administration rate of bone-modifying agents in patients with osseous mCRPC. However, real-world data also suggest an OS benefit when bone-modifying agents are used, even after controlling for possible confounding patient and tumor characteristics.

**Keywords:** mHSPC, mCRPC, skeletal events, zoledronic acid, denosumab, bisphosphonates

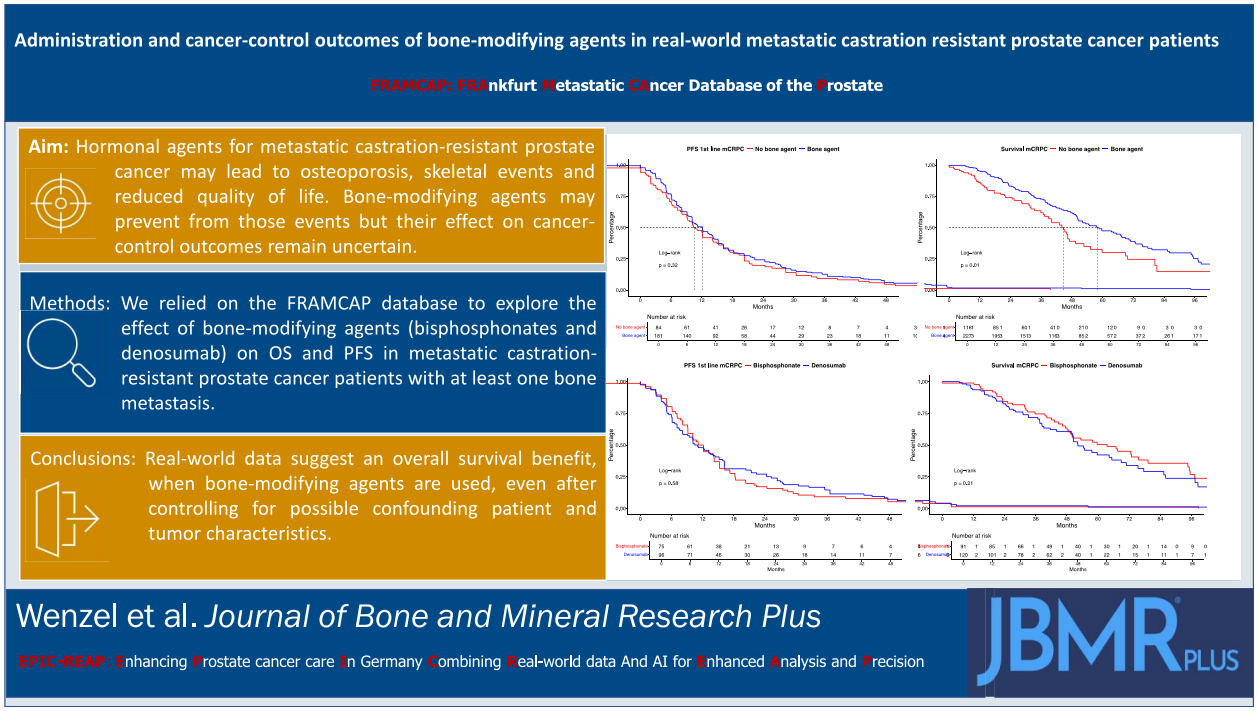
## Lay Summary

The use of bone-modifying agents is associated with better cancer-control outcomes in patients with metastatic castration-resistant prostate cancer. However, differences between the 2 types of antiresorptive treatments, bisphosphonates and denosumab, were not seen. Importantly, rates of patients receiving bone-modifying agents are relatively low and clinicians should aim to improve those rates.

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## Graphical Abstract




## Introduction

Metastatic sites of prostate cancer mainly affect the skeletal bones.[1] As the backbone of metastatic prostate cancer treatment, androgen deprivation therapy has been the standard of care for decades, and is currently combined with newly approved androgen signaling receptor inhibitors.[2–11] However, these hormonal agents are associated with an increased risk of loss of bone mineral density, osteoporosis, and skeletal events such as fractures and reduced quality of life.[12–15]

To avoid skeletal events and a reduction in quality of life, European Association of Urology guidelines strongly recommend bone-protective agents to prevent osseous complications in patients with castration-resistant prostate cancer with bone metastases.[16] These recommendations are based on prospective phase III trials, demonstrating a reduction in skeletal events for patients with metastatic castration-resistant prostate cancer (mCRPC) when bone-modifying agents are used.[17,18] Moreover, 1 post hoc analysis from 3 prospective trials in 2007 demonstrated worse overall survival in patients with prostate cancer when pathological fractures occurred.[19] Nonetheless, real-world data on cancer-control outcomes of bone-modifying agents are scant and most studies solely focused on administration rates in mCRPC, irrespective of metastatic sites.[20]

We addressed this knowledge gap and relied on our institutional metastatic prostate cancer database to investigate the effect of bone-modifying agents on cancer-control outcomes, such as progression-free and overall survival on contemporary treated patients with mCRPC with bone metastases. We hypothesized that statistically significant and clinically meaningful differences in progression-free, as well as overall survival, may be observed with the administration of bone-modifying agents for patients with mCRPC. Moreover, we also hypothesized that differences between the 2 groups of bone-modifying agents, such as bisphosphonates vs denosumab, may be observed.

## Materials and methods

### Study population

Following approval from the local ethics committee at Goethe University Hospital Frankfurt (reference number: SUG-5-2018) and in accordance with the guidelines set forth in the Declaration of Helsinki, we undertook a retrospective study focusing on all patients diagnosed with mCRPC who were treated at the Department of Urology, University Hospital Frankfurt, Germany ($n = 721$). The inclusion criteria encompassed all cases of patients with mCRPC discussed in interdisciplinary tumor conferences since 2014 and metastatic disease in at least 1 bone. Metastatic castration-resistant prostate cancer was defined in accordance with European Urology Association guideline recommendations.[16] These selection criteria yielded 529 patients with mCRPC for further analyses, of whom 420 patients had information on administration of bone-modifying agents and qualified for study inclusion.

### Bone-modifying agents

Bone-modifying agents such as bisphosphonates (eg, zoledronic acid) or denosumab were administered according to the suggested schedules, doses, and duration or adjusted according to physicians' choice.

### Statistical analysis and study endpoints

Descriptive statistics involved analyzing the occurrence and proportions of categorical variables studied, as well as determining the median values and IQRs for continuous variables. The significance of proportion disparities was evaluated using

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the chi-square and Fisher's exact test, while variations in distributions were explored using both the *t* test and Kruskal-Wallis rank-sum test.

Analyses were performed in mCRPC stage only, since European Urology Association guidelines recommend the use of bone-modifying agents only in this setting and no effect has been observed for metastatic hormone-sensitive prostate cancer.[16,21] Kaplan-Meier curve analyses graphically depicted progression-free and overall survival for patients stratified according to the administration and usage of bone-modifying agents vs non–bone-modifying agents.

Moreover, in the second set of analyses, progression-free and overall survival outcomes were stratified according to the use of bisphosphonates vs denosumab, if information was available. Finally, for both sets of analyses, univariable as well as multivariable Cox regression models were applied. As covariates, baseline patient and tumor characteristics (age at metastatic disease, Gleason score, low- vs high-volume disease according to CHAARTED criteria,[22] and local therapy to the prostate, de novo metastatic disease) were used to maximally adjust for confounding variables. For progression-free survival analyses, additional adjustment for first-line mCRPC treatment was performed, while, for overall survival analyses, additional adjustment for the number of systemic treatment lines was performed. All tests were 2-sided with a level of significance set at $p < .05$, and R software environment for statistical computing and graphics (version 2023.12.1+402) was used for all analyses.

## Results

Overall, 420 patients with mCRPC qualified for analysis in the current study, with a median follow-up of 28 months (12–49 months), at a median age of metastatic prostate cancer disease of 68 years (IQR: 62–73 years), and a median prostate-specific antigen level at mCRPC of 18 ng/mL (IQR: 6–65 ng/mL). Progression to mCRPC and the inclusion period were between years 2005 and 2024.

### Characteristics of patients with bone-modifying agents

Of all included patients with mCRPC with at least 1 bone metastasis, 60% ($n = 251$) received a bone-modifying agent vs 40% ($n = 169$) of patients without a bone-modifying agent (Table 1). Significant differences between both groups were observed regarding baseline patient and tumor characteristics. Specifically, patients who received a bone-modifying agent were younger (68 vs 69 years, $p = .033$) and received, on median, more systemic treatment lines for mCRPC (3 vs 2, $p < .001$) and had less frequently a history or an active secondary malignancy (6.9% vs 14%, $p = .028$).

Moreover, proportions of initial de novo metastatic disease were higher in patients with bone-modifying agents (72% vs 62%, $p = .04$). However, no differences were observed regarding initial metastatic burden (defined as CHAARTED high volume) and risk category (defined as LATITUDE high risk) between both compared groups (both $p \geq .2$). Finally, statistically significant differences in proportions of mCRPC first-line treatment were observed ($p = .049$). Patients with a bone-modifying agent more frequently received chemotherapy (20% vs 12%) and androgen signaling receptor inhibitors (59% vs 41%) relative to their counterparts without a bone-modifying agent. However, no differences were observed in second-line mCRPC treatment patterns. The overall rate of osteonecrosis to the jaw was 11% ($n = 26$). The rates significantly decreased within more recent years with regular dental assessment (2006–2014 vs 2018–2024: 15.4% vs 5.3%; $p = .048$).

### Oncological outcomes of patients with bone-modifying agents

In time to progression of first-line mCRPC treatment, no significant differences were observed between both compared groups, with median progression-free survival of 12 vs 11 months for patients with vs without bone-modifying agents ($p = .32$; Figure 1A). However, after further multivariable adjustments for patient and tumor characteristics, patients with bone-modifying agents harbored a significant reduced risk of progression relative to patients without bone-modifying agents (hazard ratio: 0.38, $p < .01$).

In subsequent overall survival analyses, significant differences were observed between patients with and without bone-modifying agents (Figure 1B; $p = .01$). Specifically, median overall survival was 58 vs 45 months, with a corresponding hazard ratio of 0.66 in favor of patients with bone-modifying agents. In additional multivariable-adjusted Cox regression models, the use of bone-modifying agents remained an independent protective factor for risk of death (hazard ratio: 0.37; $p < .01$).

### Characteristics of bisphosphonates vs denosumab patients

In the second step of analyses, 230 patients with mCRPC with available information were stratified according to the used medication of bone-modifying agents. Follow-up duration was longer in the bisphosphonates group compared with the denosumab group (40 vs 37 months, $p = .057$). Overall, 57% ($n = 132$) received denosumab vs 43% ($n = 98$) of patients with mCRPC receiving bisphosphonates (Table 2). Significant differences were observed in the proportions of patients with Eastern Cooperative Oncology Group status ≥2, which was higher in the bisphosphonates group (7.4% vs 2.5%, $p < .001$). Moreover, the IQR of the number of administered systemic therapies for mCRPC differed between both groups ($p < .001$), with a median of 3 administered lines in both groups.

No statistically significant or clinically meaningful differences were observed for most tumor characteristics. However, in second-line mCRPC treatment, rates of lutetium radioligand therapy was higher in the denosumab group (12% vs 5.1%), while rates of androgen signaling receptor inhibitors (35% vs 43%) and chemotherapy (23% vs 32%) were lower, but the overall distribution did not differ significantly ($p = .072$). No differences in the rates of osteonecrosis of the jaw were observed between both groups with 12% in both groups ($p > .9$).

### Oncological outcomes of bisphosphonates vs denosumab

In progression-free survival analyses, no significant differences were observed when bisphosphonates patients were compared with denosumab patients (Figure 2A; $p = .58$) with median progression-free survival of 12 and 11 months. In multivariable Cox regression models, a trend towards a

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**Table 1.** Baseline patient and tumor characteristics of 420 patients with metastatic castration-resistant prostate cancer (mCRPC) stratified according to use of a bone-modifying agent (BMA).

| Characteristic | *n* | Overall (*n* = 420)[a] | No BMA (*n* = 169; 40%)[a] | BMA (*n* = 251; 60%)[a] | *p*[b] |
|---|---|---|---|---|---|
| Age at metastatic disease, y | 405 | 68 (62, 73) | 69 (65, 74) | 68 (61, 73) | .033 |
| PSA at first-line mCRPC | 192 | 18 (6, 65) | 13 (4, 58) | 21 (6, 65) | .4 |
| PSA at 2nd line mCRPC | 205 | 47 (11, 140) | 49 (10, 183) | 41 (11, 116) | .6 |
| CRPC treatment lines | 420 | 3.00 (1.00, 4.00) | 2.00 (1.00, 3.00) | 3.00 (2.00, 4.00) | <.001 |
| Osteonecrosis of jaw | 231 | 26 (11%) | 0 (0%) | 26 (11%) | >.9 |
| No osteonecrosis | | 205 (89%) | 4 (100%) | 201 (89%) | |
| ECOG 0–1 | 267 | 255 (95%) | 111 (95%) | 144 (96%) | .4 |
| ECOG ≥2 | | 12 (4.5%) | 6 (5.1%) | 6 (4.0%) | |
| Secondary malignancy | 336 | 34 (10%) | 21 (14%) | 13 (6.9%) | .028 |
| No secondary malignancy | | 302 (90%) | 127 (86%) | 175 (93%) | |
| Gleason score | 367 | 367 | 146 | 221 | .7 |
| 6–7 | | 106 (29%) | 44 (30%) | 62 (28%) | |
| 8–10 | | 261 (71%) | 102 (70%) | 159 (72%) | |
| Local therapy RP/RT | 420 | 158 (38%) | 73 (43%) | 85 (34%) | .053 |
| No local therapy RP/RT | | 262 (62%) | 96 (57%) | 166 (66%) | |
| Visceral metastasis mHSPC | 351 | 17 (4.8%) | 6 (4.1%) | 11 (5.3%) | .6 |
| No visceral metastasis mHSPC | | 334 (95%) | 139 (96%) | 195 (95%) | |
| High-volume mHSPC | 211 | 128 (61%) | 54 (58%) | 74 (63%) | .5 |
| Low-volume mHSPC | | 83 (39%) | 39 (42%) | 44 (37%) | |
| High-risk mHSPC | 222 | 148 (67%) | 61 (62%) | 87 (70%) | .2 |
| Low-risk mHSPC | | 74 (33%) | 37 (38%) | 37 (30%) | |
| De novo mHSPC | 414 | 280 (68%) | 104 (62%) | 176 (72%) | .040 |
| Secondary mHSPC | | 134 (32%) | 64 (38%) | 70 (28%) | |
| Treatment first-line mCRPC | 420 | 420 | 169 | 251 | .049 |
| ADT monotherapy | | 27 (6.4%) | 12 (7.1%) | 15 (6.0%) | |
| Chemotherapy | | 71 (17%) | 21 (12%) | 50 (20%) | |
| ARSI | | 218 (52%) | 70 (41%) | 148 (59%) | |
| Lu-RLT | | 14 (3.3%) | 7 (4.1%) | 7 (2.8%) | |
| Radium | | 11 (2.6%) | 4 (2.4%) | 7 (2.8%) | |
| None/other/NA | | 79 (19%) | 55 (33%) | 24 (9.6%) | |
| Treatment second-line mCRPC | 420 | 420 | 169 | 251 | .5 |
| Chemotherapy | | 100 (24%) | 34 (20%) | 66 (26%) | |
| ARSI | | 129 (31%) | 40 (24%) | 89 (35%) | |
| Lu-RLT | | 38 (9.0%) | 15 (8.9%) | 23 (9.2%) | |
| Radium | | 16 (3.8%) | 5 (3.0%) | 11 (4.4%) | |
| PARPi ± ARSI | | 5 (1.2%) | 1 (0.6%) | 4 (1.6%) | |
| None/other/NA | | 132 (31%) | 74 (44%) | 58 (23%) | |

[a]Values are median (IQR) or *n* (%). [b]Kruskal-Wallis rank-sum test, Fisher's exact test, or Pearson's chi-square test were used. Abbreviations: ADT, androgen deprivation therapy; ARSI, androgen receptor signaling inhibitor; CRPC, castration-resistant prostate cancer; ECOG, Eastern Cooperative Oncology Group; Lu-RLT, lutetium-radioligand therapy; mHSPC, metastatic hormone-sensitive prostate cancer; NA, not available; PARPi, inhibitor of poly(ADP-ribose)-polymerase; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy.

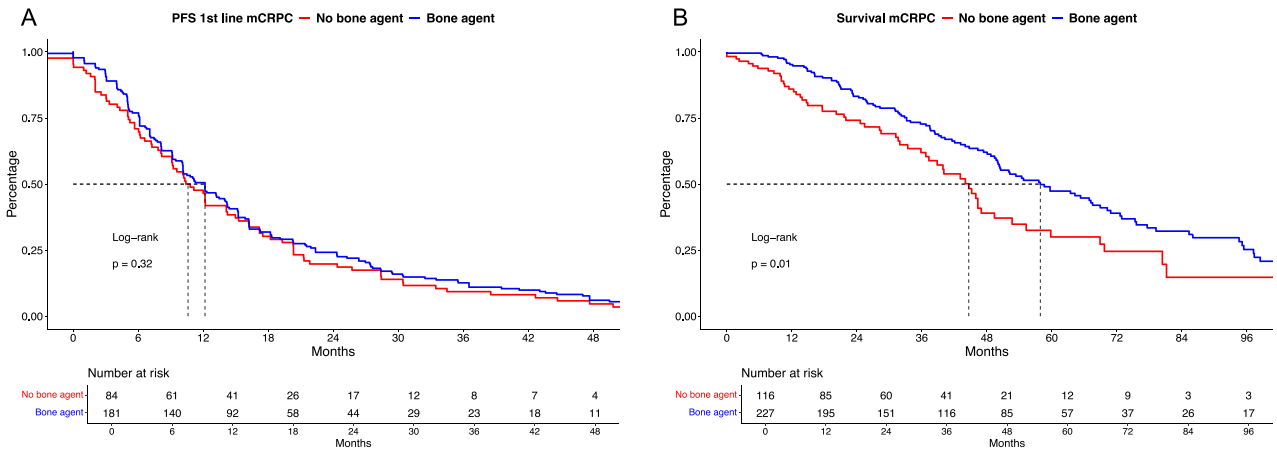



**Figure 1.** Kaplan–Meier curves depicting progression-free survival (PFS) in first-line metastatic castration-resistant prostate cancer (mCRPC; A), as well as overall survival (B) stratified according to the administration of bone-modifying agents.

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**Table 2.** Baseline patient and tumor characteristics of 230 patients with metastatic castration-resistant prostate cancer (mCRPC) stratified according to bone-modifying agents.

| Characteristic | *n* | Overall (*n* = 230)[a] | Bisphosphonates (*n* = 98; 43%)[a] | Denosumab (*n* = 132; 57%)[a] | *p*[b] |
|---|---|---|---|---|---|
| Age at metastatic disease, y | 219 | 68 (61, 73) | 68 (61, 73) | 67 (62, 73) | >.9 |
| PSA at first-line mCRPC | 110 | 19 (6, 62) | 26 (9, 63) | 16 (6, 58) | .6 |
| PSA at second-line mCRPC | 230 | 43 (12, 118) | 62 (12, 150) | 38 (14, 113) | .6 |
| CRPC treatment lines | 217 | 3.00 (2.00, 4.00) | 3.00 (3.00, 5.00) | 3.00 (2.00, 4.00) | .001 |
| ECOG ≥2 | 135 | 6 (4.4%) | 4 (7.4%) | 2 (2.5%) | <.001 |
| Secondary malignancy | 167 | 10 (6.0%) | 2 (3.4%) | 8 (7.4%) | .5 |
| Gleason score | 201 | | | | .8 |
| 6–7 | | 56 (28%) | 22 (27%) | 34 (29%) | |
| 8–10 | | 145 (72%) | 60 (73%) | 85 (71%) | |
| Local therapy RP/RT | 230 | 78 (34%) | 30 (31%) | 48 (36%) | .4 |
| Visceral metastasis mHSPC | 190 | 10 (5.3%) | 6 (8.1%) | 4 (3.4%) | .2 |
| High-volume mHSPC | 100 | 61 (61%) | 22 (61%) | 39 (61%) | >.9 |
| High-risk mHSPC | 106 | 74 (70%) | 26 (67%) | 48 (72%) | .6 |
| De novo mHSPC | 227 | 160 (70%) | 67 (68%) | 93 (72%) | .5 |
| Osteonecrosis of the jaw | 217 | 26 (12%) | 11 (12%) | 15 (12%) | >.9 |
| Treatment first-line mCRPC | 230 | | | | .8 |
| ADT monotherapy | | 15 (6.5%) | 7 (7.1%) | 8 (6.1%) | |
| Chemotherapy | | 47 (20%) | 19 (19%) | 28 (21%) | |
| ARSI | | 139 (60%) | 62 (63%) | 77 (58%) | |
| Lu-RLT | | 6 (2.6%) | 3 (3.1%) | 3 (2.3%) | |
| Radium | | 7 (3.0%) | 3 (3.1%) | 4 (3.0%) | |
| None/other/NA | | 16 (7.0%) | 4 (4.1%) | 12 (9.1%) | |
| Treatment second-line mCRPC | 230 | | | | .072 |
| Chemotherapy | | 62 (27%) | 31 (32%) | 31 (23%) | |
| ARSI | | 88 (38%) | 42 (43%) | 46 (35%) | |
| Lu-RLT | | 21 (9.1%) | 5 (5.1%) | 16 (12%) | |
| Radium | | 11 (4.8%) | 5 (5.1%) | 6 (4.5%) | |
| PARPi ± ARSI | | 3 (1.3%) | 2 (2.0%) | 1 (0.8%) | |
| None/Other/NA | | 45 (20%) | 13 (13%) | 32 (24%) | |

[a] Values are median (IQR) or *n* (%). [b] Kruskal-Wallis rank-sum test, Pearson's chi-square test, or Fisher's exact test were used. Abbreviations: ADT, androgen deprivation therapy; ARSI, androgen receptor signaling inhibitor; CRPC, castration-resistant prostate cancer; ECOG, Eastern Cooperative Oncology Group; Lu-RLT, lutetium-radioligand therapy; mHSPC, metastatic hormone-sensitive prostate cancer; NA, not available; PARPi, inhibitor of poly(ADP-ribose)-polymerase; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy.

possible protective effect of denosumab was observed (hazard ratio: 0.45; 95% CI: 0.19–1.08; $p$ = .075) relative to bisphosphonates.

In overall survival analyses (Figure 2B), also no significant differences were observed in the comparison between bisphosphonates patients and denosumab patients, with a median overall survival of 63 vs 52 months ($p$ = .21). In multivariable Cox regression models, no significant difference was observed between both groups (denosumab hazard ratio: 0.60; 95% CI: 0.26–1.38; $p$ = .23).

## Discussion

We hypothesized that statistically significant and clinically meaningful differences in progression-free, as well as overall, survival may be observed with the administration of bone-modifying agents for currently treated, real-world patients with mCRPC. Moreover, we also hypothesized that differences between the 2 groups of bone-modifying agents, such as bisphosphonates vs denosumab, may be observed. To investigate these hypotheses, we relied on our institutional tertiary-care metastatic prostate cancer database and several noteworthy observations.

First, we observed that, in a real-world setting, 60% of patients with bone metastasis at mCRPC stage receive a bone-modifying agent. Moreover, we observed that significant differences can be shown when patients with vs those without bone-modifying agents are compared. Specially, patients with bone-modifying agents were younger and harbored less frequent proportions of concomitant comorbidities (measured as secondary cancers) and received more systemic therapy lines. Moreover, patients with bone-modifying agents harbored higher rates of de novo metastatic prostate cancer than patients who did not receive a bone-modifying agent. Comparing these findings with previously published reports, our reported rate of bone-modifying agent administration is slightly lower than those reported by Mitchell et al[20] using epidemiological data from the SEER (Surveillance, Epidemiology, and End Results) database. Here, a 68% rate of bone-modifying agent use was observed in 1034 patients with mCRPC with bone metastases. An even lower rate of approximately 33% was seen in a real-world cohort of the Australian mCRPC database.[23] Moreover, only 40% of patients with mCRPC received bone-modifying agents in the prospective phase III trial of the comparison between radium-223 plus abiraterone vs abiraterone alone.[24] However, a post hoc analysis showed that bone-modifying agents reduced the rate of bone fractures in both trial arms. All of these provided rates are lower than expected in real-world and trial-selected patients with mCRPC and emphasize the urgent need for better clinician and patient education regarding bone health to prevent bone fractures or other skeletal events, and even prolong overall survival. It is especially of note that the majority of patients with mCRPC receive no bone-modifying agent prior to their first skeletal event.[25] Moreover, our data should

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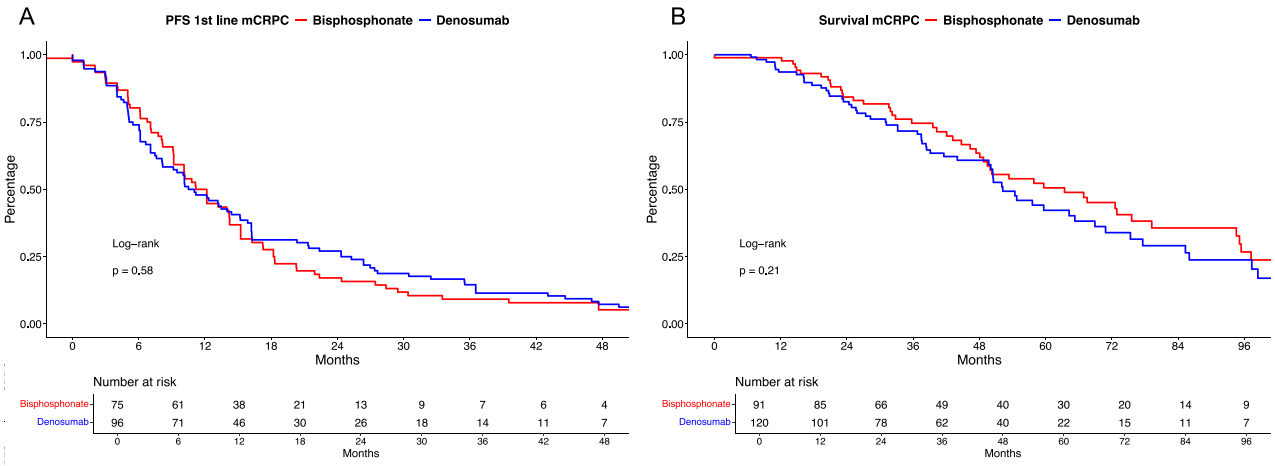



**Figure 2.** Kaplan–Meier curves depicting progression-free survival (PFS) in first-line metastatic castration-resistant prostate cancer (mCRPC; A), as well as overall survival (B) stratified according to the administered bone-modifying agents: bisphosphonates vs denosumab.

sensitize clinicians that patients with secondary malignancies may be undertreated regarding bone-modifying agents.

Second, when cancer-control outcomes were compared between patients with and those without bone-modifying agents, no difference in first-line progression-free survival was observed. However, after additional multivariable adjustment for confounding patient baseline and tumor characteristics, osteoprotection was shown to be a predictor of longer progression-free survival. These findings may be interpreted as a surrogate for skeletal events, since most skeletal events such as bone fractures may occur with progressive disease and affect 22% to 42% of patients with mCRPC with bone metastases.[23,26,27] Moreover, in overall survival analyses, patients treated with bone-modifying agents harbored significantly better survival (median overall survival: 58 vs 45 months) with a 34% reduced risk of death. Additionally, these findings were further validated in our multivariable Cox regression model adjusting for possible confounding variables and yielded an even higher protective effect (hazard ratio: 0.37), which may lead to the interpretation of statistically robust and clinically important findings. These findings are additionally supported by the observations of Saad et al,[19] incorporating data from 3 prospective phase III trials and reporting a 29% higher risk of death in patients with prostate cancer with skeletal events. Unfortunately, the current study and the study by Saad et al could not distinguish between cancer-specific and other-cause mortality. Explanations of better cancer-control outcomes with bone-modifying agents may the immunomodulating effect in bone metastases, as previously described in other cancer entities, as well as lower rates of fractures, hospital stays, and reduced quality of life.[28]

Third, when further stratification was performed according to the bone-modifying agent used (bisphosphonates vs denosumab), we observed that 57% of patients received denosumab and 43% received bisphosphonates. Moreover, differences can be observed in proportions of frailty Eastern Cooperative Oncology Group status ≥2, which was higher in the bisphosphonates group. Conversely, the number of systemic treatment lines was lower and follow-up was shorter in the denosumab group. These findings are not surprising since the approval of denosumab in Europe was in 2011, with its wide adoption in recent years.[20] Moreover, when rates of osteonecrosis of the jaw were compared, no differences between both groups were found, with an overall rate of 12% in both groups, which was lower compared with recently published cohorts of patients with metastatic prostate and kidney cancer, with a total of 23% and 25%, respectively.[29,30] Other studies reported a comparable risk of 9.8% within 48 months of treatment.[31] However, this risk can be further decreased, when, prior to the administration of bone-modifying agents, dental assessment is performed.[32] When we adopted this strategy in 2018, our rate of osteonecrosis of the jaw significantly decreased.

Finally, when cancer-control outcomes were compared between bisphosphonates and denosumab, no differences in progression-free survival of first-line mCRPC, as well as overall survival, were observed. However, in multivariable Cox regression models, a trend towards a beneficial effect of denosumab over bisphosphonates for progression-free survival outcomes may exist (hazard ratio: 0.45; 95% CI: 0.19–1.08; $p$ = .075). Compared with previous studies, the prospective phase III STAMPEDE trial has demonstrated a 18% risk reduction of skeletal events with denosumab in comparison to bisphosphonates.[17] Similar results were observed when 5543 patients from 3 phase III trials with prostate, breast, and other solid metastatic tumors were grouped, with an identical hazard ratio of 0.82, as well as in a Cochrane systematic review.[18,33]

The current retrospective study analyzing metastatic prostate cancer data is subject to several limitations that must be considered when interpreting the results. In particular, the study is constrained by missing data for some variables, which may impact the completeness and reliability of the findings in comparison to variables or survival outcomes. Additionally, reliance on medical records introduces the possibility of inaccuracies or gaps that could further influence the results. Second, selection bias cannot be ruled out, as the study population was confined to patients within the healthcare system of a tertiary-care medical hospital under scrutiny. Moreover, there are observable and unobservable differences in patient and tumor characteristics between the groups with and without bone-modifying agents, as well as the subgroups of denosumab and bisphosphonates, such as possibly duration of administration, doses, and schedules. Even in multivariable regressions, these differences might only be partly adjustable, which might lead to a further selection

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bias. Additionally, the analysis might not have adequately addressed all confounding variables, such as underlying health conditions or socioeconomic status, which could impact disease outcomes. Some of the performed analyses may lack a sufficient sample size. Finally, no further information on adverse side effects, such as skeletal-related events, was available. Ideally, prospective trials will further investigate based upon our findings.

Taken together, the current study analyzing the administration and use of bone-modifying agents in real-world patients with mCRPC with bone metastasis showed a relatively low rate of bone-modifying agents. Conversely, the use of bone-modifying agents showed better cancer-control outcomes than in patients without any bone-modifying agents. No differences in overall survival were observed between the comparison of bisphosphonates and denosumab, while denosumab showed numerically better results in progression-free survival analysis after adjusting for covariates. Event rates of osteonecrosis to the jaw were low in both groups. Consequently, clinical efforts should be made to increase bone-modifying agent administration rates for better cancer-control outcomes.

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## Author contributions

Mike Wenzel (Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Writing—original draft), Benedikt Hoeh (Conceptualization, Formal analysis, Project administration, Writing—original draft), Clara Humke (Methodology, Project administration, Visualization), Maria Welte (Project administration, Writing—original draft), Cristina Cano Garcia (Methodology, Project administration, Writing—original draft), Carolin Siech (Data curation, Formal analysis), Fred Saad (Supervision, Validation, Writing—review & editing), Pierre I. Karakiewcz (Supervision, Validation, Writing—review & editing), Derya Tilki (Supervision, Validation, Writing—review & editing), Thomas Steuber (Supervision, Validation, Writing—review & editing), Markus Graefen (Supervision, Validation, Writing—review & editing), Miriam Traumann (Methodology, Project administration, Validation), Felix K.H. Chun (Supervision, Validation, Writing—review & editing), and Philipp Mandel (Conceptualization, Data curation, Validation, Writing—original draft).

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## Conflicts of interest

None declared.

## Data availability

Data are available for bona fide researchers who request it from the authors.

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