# Incidence of Medication-Related Osteonecrosis of the Jaw in Patients With Breast Cancer During a 20-Year Follow-Up: A Population-Based Multicenter Retrospective Study

Christine Brunner, MD[1]; Marjan Arvandi, MD, PhD[2]; Christian Marth, MD, Prof[1]; Daniel Egle, MD[1]; Florentina Baumgart, MD[1]; Miriam Emmelheinz, MD[1]; Benjamin Walch, MD[3]; Johanna Lercher, MD[3]; Claudia Iannetti, MD[4]; Ewald Wöll, MD[5]; Agnes Pechlaner, MD[5]; August Zabernigg, MD[6]; Birgit Volgger, MD[7]; Maria Castellan, MD[7]; Oliver Tibor Andraschofsky, MD[8]; Alice Markl, MD[9]; Michael Hubalek, MD[10]; Michael Schnallinger, MD[11]; Sibylle Puntscher, MD[2]; Uwe Siebert, MD, MPH, MSc, ScD, Prof[2,12,13]; Sebastian Schönherr, MD[14]; Lukas Forer, PhD[14]; Emanuel Bruckmoser, MD[15]; and Johannes Laimer, MD[3]

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## ABSTRACT

**PURPOSE** Medication-related osteonecrosis of the jaw (MRONJ) is one of the most important toxicities of antiresorptive therapy, which is standard practice for patients with breast cancer and bone metastases. However, the population-based incidence of MRONJ is not well established. We therefore performed a retrospective multicenter study to assess the incidence for a whole Austrian federal state (Tyrol).

**MATERIALS AND METHODS** This retrospective multicenter study was conducted between 2000 and 2020 at all nine breast centers across Tyrol, Austria. Using the cancer registry, the total Tyrolean population was screened for all patients with breast cancer. All patients with breast cancer and bone metastases receiving antiresorptive therapy were finally included in the study.

**RESULTS** From 8,860 patients initially screened, 639 individuals were eligible and included in our study. Patients received antiresorptive therapy once per month without de-escalation of therapy. MRONJ was diagnosed in 56 (8.8%, 95% CI, 6.6 to 11.0) patients. The incidence of MRONJ was 11.6% (95% CI, 8.0 to 15.3) in individuals treated with denosumab only, 2.8% (95% CI, 0.7 to 4.8) in those treated with bisphosphonates only, and 16.3% (95% CI, 8.8 to 23.9) in the group receiving bisphosphonates followed by denosumab. Individuals developed MRONJ significantly earlier when treated with denosumab. Time to MRONJ after treatment initiation was 4.6 years for individuals treated with denosumab only, 5.1 years for individuals treated with bisphosphonates only, and 8.4 years for individuals treated with both consecutively.

**CONCLUSION** MRONJ incidence in breast cancer patients with bone metastases was found to be considerably higher, especially for patients receiving denosumab, when compared with available data in the literature. Additionally, patients treated with denosumab developed MRONJ significantly earlier.

ACCOMPANYING CONTENT

Appendix

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## INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is a potentially severe and often quality-of-life–affecting condition for patients with osseous metastasized breast cancer.[1] As a drug side effect, MRONJ is mainly triggered by antiresorptive treatment including bisphosphonates and the monoclonal antibody denosumab.[2]

The risk to develop MRONJ depends on a multitude of different factors, and highly varying figures are reported in the international literature ranging from 1% to 17%.[3] There is abundant evidence that the duration of antiresorptive treatment has a significant influence on MRONJ incidence in that a longer duration of antiresorptive treatment increases the risk for MRONJ regardless of therapy indications.[4,5] Further risk factors for MRONJ include dentures[6] and preexisting inflammatory dental disease such as periodontitis or periapical pathology.[7,8]

In previous studies including a multicenter study with 3,360 patients and a meta-analysis of 15 studies, MRONJ was confirmed in 0.52%-1.7% of patients receiving bisphosphonates.[9,10] A considerably higher number was

## CONTEXT

**Key Objective**

What is the population-based incidence of medication-related osteonecrosis of the jaw (MRONJ) in breast cancer patients with bone metastases?

**Knowledge Generated**

MRONJ was diagnosed in 8.8% patients. The cumulative incidence of MRONJ was 11.6% in patients treated with denosumab only, 2.8% with bisphosphonates only, and 16.3% with bisphosphonates followed by denosumab. In this study providing real-world data, the MRONJ incidence in breast cancer patients with bone metastases was found to be considerably higher, when compared with available data in the literature. Statistical analyses revealed a significant difference in MRONJ incidence depending on the type of antiresorptive treatment.

**Relevance *(K.D. Miller)***

Clinical trials of skeletal protective therapy typically provided therapy for only 2 years and reported a much lower rate of MRONJ. Clinicians should be aware of this increased risk with longer-term therapy, especially with monthly therapy. The extent to which reducing the frequency of administration, a common clinical practice, alters this risk is unknown.*

*Relevance section written by *JCO* Senior Deputy Editor Kathy D. Miller, MD.



reported in an international, multicenter, randomized, controlled phase III trial evaluating adjuvant denosumab in 4,509 patients with early breast cancer. MRONJ occurred in 122 of 2,241 women corresponding to 5.4%.[11] In a retrospective study including patients with bone metastases, the multivariate analysis revealed that denosumab was associated with a significantly higher risk of developing MRONJ compared with bisphosphonates.[3]

The heterogeneity of evaluated patient collectives in the international literature in addition to a presumed underreporting makes it difficult to reliably determine the overall risk for developing MRONJ.[12] Therefore, a retrospective population-based approach as presented in our study may allow for a more precise evaluation of the incidence of MRONJ, especially for patients with different antiresorptive therapies such as bisphosphonates or denosumab.

Our main objective was to assess the population-based incidence of MRONJ in breast cancer patients with bone metastases receiving antiresorptive therapy for a whole Austrian state with 771,000 residents. Furthermore, we wanted to compare the risk of triggering MRONJ for the two most commonly used antiresorptive agents, that is, bisphosphonates and denosumab.

## MATERIAL AND METHODS

### Study Design

In this retrospective multicenter observational study, we were able to screen 100% of patients with breast cancer of the Austrian state Tyrol from 2000 to 2020 using the local cancer registry.[13] This database works via an obligatory automated process by analyzing the International Classification of Diseases code-10 codes used in every hospital in Austria and provides a complete and thorough database of all patients with cancer.

The data for the retrospective analysis was collected using an electronic case report form (e-CRF) and managed via the web-based database AskiMed.[14] AskiMed is an e-CRF software and cloud-based platform for data collection and data management. It facilitates standardized data collection for studies with multiple centers involved. This study gathered data from all nine breast treatment centers in Tyrol. Characteristic for this state is that about two thirds of patients live in rural areas and traditionally tend to have a long residence time in one place. Therefore, follow-up rates were comparatively high in our patient collective.

All individuals diagnosed with breast cancer and bone metastases (primary as well as secondary) between 2000 and 2020, who received antiresorptive treatment, were included in the study. Exclusion criteria comprised patients with no bone metastases, unknown MRONJ status, no antiresorptive therapy, or patients for whom no data were available. Patients started receiving antiresorptive therapy as soon as bone metastases were diagnosed and until last follow-up or death.

According to guidelines,[15] antiresorptive treatment of bone metastases before 2010 consisted of 4 mg zoledronic acid once per month intravenously and then, once per month subcutaneous administration of 120 mg denosumab became standard of care. Consequently, apart from patients

receiving only one class of antiresorptive therapy, our study also includes a third group, that is, patients having received bisphosphonates and denosumab sequentially.

Basic characteristics gathered from the study population included age, BMI, menopausal status, primary versus secondary bone metastases, type of antiresorptive treatment (bisphosphonates and/or denosumab), other targeted therapies commonly used in breast cancer therapy (chemotherapy, antihormonal therapy, and targeted therapy), and comorbidities (type 2 diabetes mellitus and osteoporosis).

Our primary outcome was the population-based incidence of MRONJ. Secondary outcomes included time from cancer diagnosis to MRONJ, and correlation between antiresorptive therapy and risk of MRONJ. Once the physician in charge of the oncologic treatment (including antiresorptives) had the suspicion of a potentially emerging MRONJ, the respective patients were referred to the outpatient clinic of the Cranio-Maxillofacial and Oral Surgery Department at the Medical University of Innsbruck (Austria) where they were examined by an experienced specialist. After the required clinical and radiological examinations in addition to a histologic sample to rule out a potential tumor, patients were then classified and—if MRONJ was diagnosed—treated accordingly.

### Statistical Analysis

Descriptive statistics were used to describe patient characteristics. Statistical tests were performed to identify statistically significant differences between the distribution of the various characteristics in the three antiresorptive treatment groups (bisphosphonates only, denosumab only, and bisphosphonates and denosumab sequentially). Statistical significance was tested using the chi-squared test for categorical variables and the Mann–Whitney *U*-test (patients with or without MRONJ) or the Kruskal-Wallis test (three treatment groups) for continuous variables because of the non-normal distribution of the variables.

The incidences of MRONJ were calculated and compared between the treatment groups. Gray's test was used to compare the cumulative incidence curves across the three treatment groups. Furthermore, two different outcome regression analyses were performed for the main outcome MRONJ. First, a logistic regression analysis was conducted considering MRONJ as a binary variable (MRONJ occurrence) over the follow-up, expressing the treatment effect on MRONJ as odds ratio (OR) with a 95% CI. Second, a Cox proportional hazard model considered MRONJ as a time-to-event variable during the period of different antiresorptive therapies, expressing the treatment effect on MRONJ as hazard ratio (HR) with 95% CI. The proportional hazard assumption was tested using the −2LL plot and interactions with time.

After a descriptive crude analysis, the primary regressions were adjusted for all potential confounders at baseline (ie, initiation of treatment). Predictors of MRONJ occurrence with a significance level below 0.2 were considered as potential confounders in the multivariable regression models. In sensitivity analyses (SA), other selection criteria for the selection of potential confounders have been used: (SA1) all variables with a significance level below 0.05 or without missing values, (SA2) variables with a significance level below 0.05, (SA3) only variables with a significance level below 0.2 that did not have missing values, and (SA4) only age was considered as the most important potential baseline confounder. To be able to compare the effect of the different treatments on the harm outcome MRONJ with the treatment effect on the benefit outcome overall survival, Kaplan-Meier curves for overall survival after first diagnosis over the entire study period in all three treatment groups were compared using the log-rank test.

Data analysis was performed using the statistical software package SAS version 9.4 (SAS Institute, Inc, Cary, NC). The significance level of all analyses of treatment effects was set at a $P < .05$.

## RESULTS

### Participants Characteristics

A total of 8,860 individuals were screened for eligibility, of whom 639 were included in this study (Fig 1). Of these individuals, 290 had primary bone metastases (metastases already present at the time of breast cancer diagnosis) and 349 participants had secondary bone metastases (metastases occurring during the course of the tumor disease). Overall, 8,221 individuals were excluded for the following reasons: no bone metastases in 8,065 individuals, no antiresorptive treatment in 126 individuals, unknown MRONJ status in 29 individuals, and missing data in one individual.

Table 1 shows the descriptive statistics of the patient collective separately for patients with and without MRONJ. Of the 639 patients included in this analysis, 292 (45.7%) were treated with denosumab only, 255 (39.9%) with bisphosphonates only, and 92 (14.4%) with bisphosphonates and denosumab sequentially.

During the whole study, patients received their therapies once per month, without de-escalation of therapy. Therefore, there is a direct correlation between time and cumulative dose.

### Incidence of MRONJ

MRONJ was diagnosed in 56 (8.8%, 95% CI, 6.6 to 1.0) patients. The cumulative incidence of MRONJ was 11.6% (95% CI, 8.0 to 15.3) in patients treated with denosumab only, 2.8% (95% CI, 0.7 to 4.7) with bisphosphonates only, and 16.3% (95% CI, 8.8 to 23.9) with bisphosphonates followed by denosumab (Fig 2).

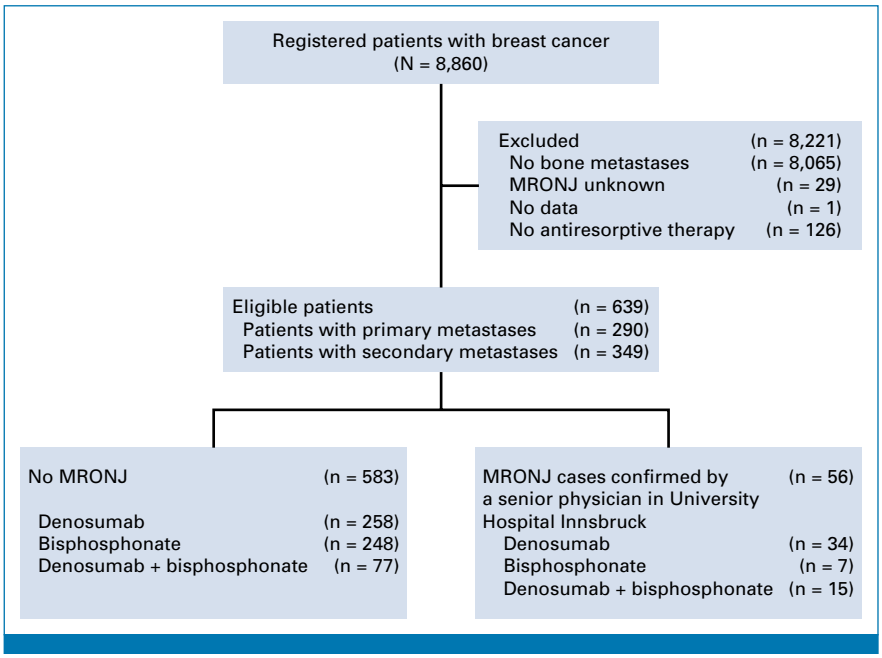


**FIG 1.** CONSORT diagram. MRONJ, medication-related osteonecrosis of the jaw.



As shown in figure and Table 2, MRONJ development significantly differed over time depending on the type of antiresorptive therapy administered (Gray's test, $P < .0001$). In the MRONJ cohort, the median ($Q_1$-$Q_3$) time to MRONJ after treatment initiation was 4.6 (1.6-9.6) years for individuals treated with denosumab only, 8.4 (5.3-9.6) years for individuals treated with bisphosphonates followed by denosumab, and 5.1 (2.9-7.1) years for individuals treated with bisphosphonates only. Details on patient's dental disease are provided in Appendix Table A1 (online only).

## ORs of MRONJ Occurrence

Our main analysis showed a statistically significant higher risk of MRONJ occurrence between patients receiving only denosumab and patients receiving both denosumab and bisphosphonate compared with those receiving only bisphosphonate.

Using treatment with bisphosphonates only as the reference category, the crude ORs for MRONJ occurrence from the logistic regression for denosumab was 4.7 (95% CI, 2.0 to 10.7), and 6.9 (95% CI, 2.7 to 17.5) for sequential bisphosphonate and denosumab therapy. We identified the following potential confounders: age at diagnosis, menopausal status, primary or secondary metastases, osteoporosis, use of corticosteroids, and HER2-positive, hormone receptor–positive, and triple-negative breast cancer. On the basis of the analysis adjusted for these confounders, the adjusted ORs were 18.8 (95% CI, 2.4 to 145.2) for denosumab and 17.8 (95% CI, 2.2 to 147.5) for sequential bisphosphonate and denosumab therapy.

In the SAs 1-4, adjusted ORs ranged from 4.8 to 6.7 for patients with denosumab, and from 6.3 to 7.5 for patients with sequential bisphosphonate and denosumab therapy for the different analyses, indicating robust results regarding the direction of the effect. The results for the SA1-SA4 are shown in the Appendix Table A2.

## Time to MRONJ Occurrence

The crude HR from the Cox model for the comparative effect on time from cancer diagnosis to MRONJ of denosumab and sequential bisphosphonate/denosumab treatment compared with bisphosphonates only were 8.6 (95% CI, 3.5 to 21.4) and 1.2 (95% CI, 0.5 to 2.9), respectively. On the basis of the adjusted Cox analysis for the potential confounders with a significance level below 0.2, patients treated with denosumab only and denosumab after bisphosphonates had HRs of 60.8 (95% CI, 6.4 to 577.6) and 5.7 (95% CI, 0.67 to 48.9), respectively, in comparison with bisphosphonates only.

In the SA 1-4 (provided in Appendix Table A2), adjusted HRs ranged from 8.7 to 14.5 for denosumab only, and from 0.99 to 1.8 for denosumab after bisphosphonates, indicating relatively robust results regarding the direction of the effect. The assumption of proportional hazards was not rejected.

## Overall Survival of Different Treatment Groups

Comparing the Kaplan-Meier curves across the three treatment groups (Fig 3) revealed statistically significant differences between the survival curves along the entire study period in the whole study population (log-rank test;

**TABLE 1.** Descriptive Statistics According to MRONJ Status

| Patient Characteristic | No MRONJ (n = 583) | MRONJ (n = 56) | Total (n = 639) | *P* |
|---|---|---|---|---|
| Age, years, median (Q1-Q3) | 62.6 (50.4-73.2) | 59.1 (45.7-67.0) | 61.8 (50.1-72.9) | .0124[a] |
| Menopausal status, No. (%) | | | | .763[b] |
| Premenopausal | 120 (24.6) | 12 (26.7) | 132 (24.8) | |
| Postmenopausal | 367 (75.4) | 33 (73.3) | 400 (75.2) | |
| BMI, No. (%) | | | | .140[b] |
| Underweight (BMI < 19) | 22 (5.7) | 0 (0.0) | 22 (5.1) | |
| Normal weight (19 < BMI < 25) | 168 (43.6) | 17 (37.8) | 185 (43.0) | |
| Overweight (BMI > 25) | 195 (50.7) | 28 (62.2) | 223 (51.9) | |
| Comorbidities, No. (%) | | | | |
| Diabetes type 2 | 51 (9.1) | 7 (12.7) | 58 (9.4) | .383[b] |
| Osteoporosis | 99 (20.1) | 7 (13.5) | 106 (19.4) | .251[b] |
| Metastasis, No. (%) | | | | .468[b] |
| Primary metastases | 262 (44.9) | 28 (50.0) | 290 (45.4) | |
| Secondary metastases | 321 (55.1) | 28 (50.0) | 349 (54.6) | |
| Tumor IHC, No. (%) | | | | |
| Hormone receptor–positive | 361 (61.9) | 44 (78.6) | 405 (75.0) | .092[b] |
| HER2-positive | 116 (21.0) | 11 (20.0) | 127 (20.9) | .860[b] |
| Triple-negative | 145 (24.9) | 7 (12.5) | 152 (23.8) | .038[b] |
| Antiresorptive therapy, No. (%) | | | | <.0001[b] |
| Denosumab only | 258 (44.3) | 34 (60.7) | 292 (45.7) | |
| Bisphosphonates only | 248 (42.5) | 7 (12.5) | 255 (39.9) | |
| Bisphosphonates and denosumab sequentially | 77 (13.2) | 15 (26.8) | 92 (14.4) | |

Abbreviations: HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MRONJ, medication-related osteonecrosis of the jaw; Q, quartile.
[a]Mann-Whitney *U* test.
[b]Chi-squared.



$P < .001$). Comparing the overall survival of the different treatment groups in a pairwise approach, a statistically significant difference in overall survival was identified when patients who received denosumab only were compared with patients who received bisphosphonates only (log-rank test; $P = .0018$) and with patients who received both treatments sequentially (log-rank test; $P < .001$).

The median overall survival after diagnosis (Fig 3) for patients treated with denosumab only was 7.9 years, for patients treated with only bisphosphonates 5.6 years, and for patients treated with bisphosphonates followed by denosumab 10.7 years. The HRs from the Cox model for the effect of the treatment group on survival time in patients receiving denosumab only and in patients receiving bisphosphonates followed by denosumab were 0.68 (95% CI, 0.54 to 0.85) and 0.50 (95% CI, 0.36 to 0.7), respectively, compared with patients treated with bisphosphonates only as the reference group.

## DISCUSSION

In this retrospective, population-based, multicenter study investigating the incidence on MRONJ overall as well as depending on different treatment protocols, the cumulative incidence of MRONJ in patients with breast cancer suffering from bone metastases was shown to be considerably higher (8.8% overall) compared with data published in the international literature so far.[9-11] This is an important finding since MRONJ can severely affect the quality of life in this highly vulnerable patient collective. Statistical analyses revealed a significant difference in MRONJ incidence depending on the type of antiresorptive treatment in our cohort. The lowest MRONJ incidence was found in individuals who received bisphosphonates only (2.8%), whereas the incidence of MRONJ was 11.6% in patients treated with denosumab only. Thus, patients in our cohort on bisphosphonates only were significantly less likely to develop MRONJ compared with individuals on denosumab only.

The highest incidence was seen in patients receiving both bisphosphonates and denosumab sequentially (16.3%). These findings are in accordance with other publications in the international literature.[3,16] Apart from the type of antiresorptive medication, longer treatment duration was identified as a risk factor significantly increasing MRONJ incidence. An increased efficacy of antiresorptive treatment

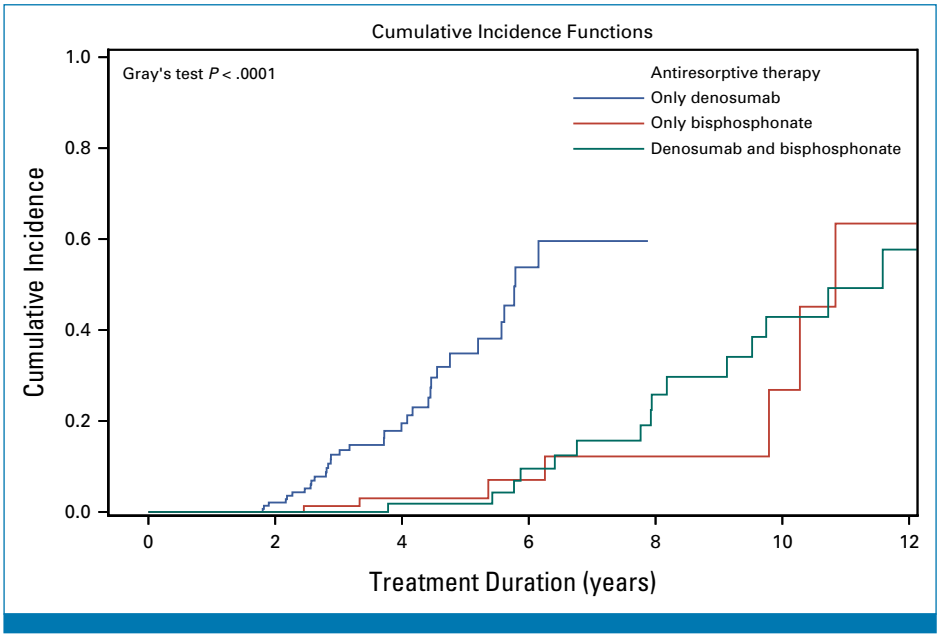


**FIG 2.** Cumulative incidence of MRONJ in the different treatment groups over the treatment period. MRONJ, medication-related osteonecrosis of the jaw.



together with improved tumor treatment options might therefore result in higher MRONJ rates.

In accordance with guidelines applicable during the whole study period (2000-2020), patients received a dose once per month of antiresorptives without de-escalation regarding the frequency of denosumab or bisphosphonates. For denosumab, current treatment protocols still favor a once per month dosing scheme, whereas a de-escalating approach is now recommended for bisphosphonates. The high frequency with continuous therapy once per month of antiresorptives may have potentially contributed to the relatively high MRONJ incidence found in our study.

To the best of our knowledge, there is only one study providing real-word data in a long-term follow-up setting. In this 9-year regional-wide survey deploying the North-Western Italy Cancer Network, the number and the main characteristics of MRONJ cases among patients with myeloma/cancer were evaluated. The authors reported a median time to MRONJ of 17, 19, or 40 months depending on the type of antiresorptive therapy.[17]

This is a crucial finding as many studies, like, for example, two major studies, had a follow-up of up to a 1 or 2 years.[18,19] One of the longest follow-up periods we found were two studies, which both followed patients for 5 years. [9,11]

Considering the time to MRONJ data found in the Italian study and our study, it is very likely that clinical trials with follow-up periods of 1 or 2 years could miss a substantial part of MRONJ cases.[18,19] Furthermore, many clinical studies do not include all patients with preexisting conditions and therefore do not represent real-word data as our study does.

For a comprehensive evaluation of key aspects in our patient collective including benefits and harms, the assessment and discussion of overall survival is essential. Comparison of the respective Kaplan-Meier curves showed a statistically significant difference in overall survival rates over the entire study period in the whole study group regarding different antiresorptive treatment protocols (log-rank test; $P < .001$; Fig 3). In our cohort, median overall survival for patients treated with denosumab only was 8 years, for patients treated with only bisphosphonates 6 years, and for patients

**TABLE 2.** Descriptive Statistics per Therapy

| Time Intervals and Duration | Denosumab (n = 292) | Bisphosphonates (n = 255) | Bisphosphonates and Denosumab (n = 92) | *P* |
|---|---|---|---|---|
| Time from cancer diagnosis to MRONJ, years, median (range; Q1-Q3) | 4.6 (17.7; 1.6-9.6) (n = 30; 4 missing) | 5.1 (5.7; 2.9-7.1) (n = 4; 3 missing) | 8.4 (15.4; 5.3-9.6) (n = 12; 3 missing) | .249[a] |
| Treatment duration in years, median (range; Q1-Q3) | 2.1 (7.9; 1-3.4) (n = 265; 27 missing) | 1.5 (13; 0.7-3.2) (n = 233; 22 missing) | 5.2 (20; 3-8) (n = 85; 7 missing) | <.0001[a] |

Abbreviations: MRONJ, medication-related osteonecrosis of the jaw; n, number; Q, quartile.
[a]Kruskal-Wallis test.

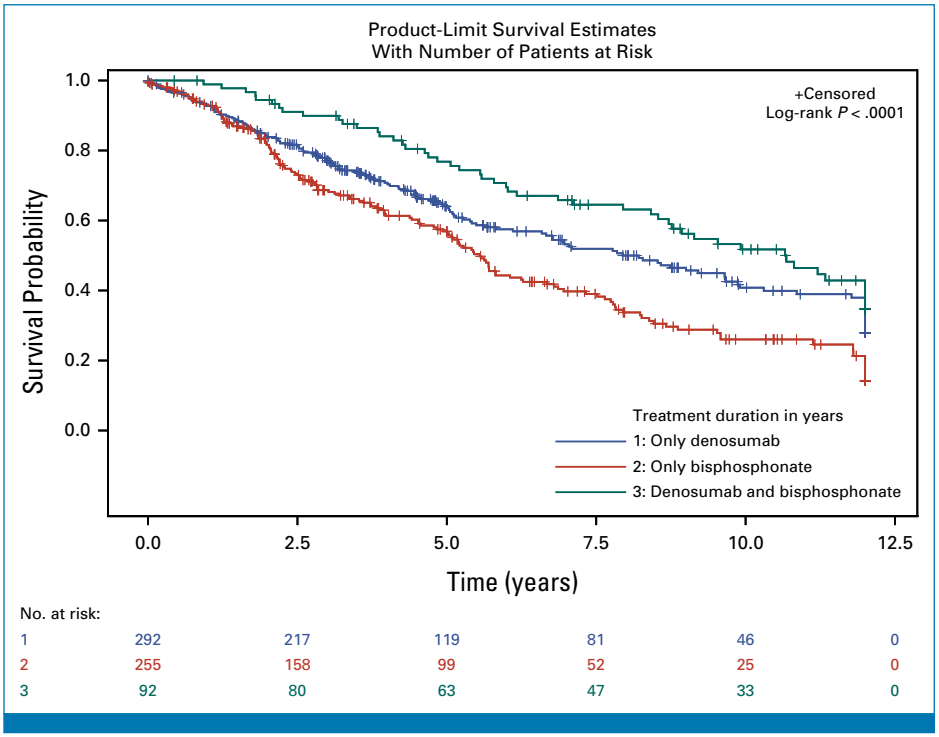


**FIG 3.** Kaplan-Meier curves for overall survival since first diagnosis in the treatment groups (truncated to 12 years).



treated with bisphosphonates followed by denosumab 11 years.

Our observations revealed a significant correlation between an antiresorptive treatment protocol including denosumab (alone or after bisphosphonates) and a higher overall survival. This needs to be interpreted with great caution. The introduction of denosumab in 2010 and its implementation into oncologic treatment protocols coincided with significant changes and progress in breast cancer therapy. Our analysis showed that the majority of MRONJ cases developed within 5 years of antiresorptive treatment initiation, and that patients often decease years after MRONJ occurrence. Generally speaking, patients do not die from MRONJ but rather from tumor progression and related complications.

This study has several limitations. First, as with all observational studies, there is an inherent risk of residual as well as time-varying confounding since variables—as a matter of principle—cannot be controlled in a retrospective design. However, of 8,860 individuals initially screened, there were only 29 patients with unknown MRONJ status, and only one patient for whom no data were available. We do not see a connection between the higher incidence and the geographical and social factors in Tyrol, but the factors as mentioned above facilitated long-term and thorough follow-up. In combination with the support of a state-wide tumor register and a reliable e-CRF database, it can be assumed that our study provides a comparatively accurate assessment of MRONJ incidence within the limits of this study design when controlled for confounding.

Second, systemic treatment protocols for breast cancer patients with bone metastases have considerably changed over the past decade. Apart from changes in oncologic therapy, denosumab was introduced in 2010 only and then incorporated into standard treatment protocols for patients with metastasized breast cancer. Since our investigation comprises a period of two decades starting in the year 2000, there is an unavoidable heterogeneity with regard to both anticancer as well as antiresorptive medication. However, as depicted in the overall survival Kaplan-Meier curves, MRONJ seems to occur frequently within the first 5 years after initiation of antiresorptive therapy. Individuals in our cohort having received novel anticancer treatments such as denosumab had a higher overall survival but were at greater risk for developing MRONJ.

In conclusion, our study revealed significantly higher MRONJ incidence rates compared with most of the international literature. Consequently, all patients scheduled for antiresorptive therapy should undergo examination in a dental office (or ideally MRONJ clinic) to diagnose and—if indicated—eliminate dentoalveolar pathologies before initiation of antiresorptive treatment. Patients must be made aware of this potential adverse event of the drug and be

educated accordingly. The item dental examination should be on the pretreatment checklist of every clinician potentially prescribing or administering antiresorptive therapy. Dental follow-up visits should be scheduled on a regular basis to provide adjusted dental care and—in case of an emerging MRONJ—to spot first signs and symptoms of MRONJ and take appropriate actions accordingly. Although tumor survival rates and avoidance of primary disease complications remain the main concern in oncology, the considerably higher risk of MRONJ should also be taken into consideration when treating patients with antiresorptive therapy.


## AFFILIATIONS

[1]Department of Obstetrics and Gynecology, Medical University of Innsbruck, Innsbruck, Austria
[2]Department of Public Health, Health Services Research and Health Technology Assessment, Medical Decision Making and Health Technology Assessment, Institute of Public Health, UMIT TIROL—University for Health Sciences and Technology, Hall in Tirol, Austria
[3]Department of Cranio-Maxillofacial and Oral Surgery, Medical University of Innsbruck, Innsbruck, Austria
[4]Department of Visceral, Transplant and Thoracic Surgery (VTT), Center of Operative Medicine, Medical University of Innsbruck, Innsbruck, Austria
[5]Department of Internal Medicine, St Vinzenz Hospital, Zams, Austria
[6]Department of Internal Medicine, County Hospital Kufstein, Kufstein, Austria
[7]Department of Obstetrics and Gynecology, County Hospital Lienz, Lienz, Austria
[8]Department of Obstetrics and Gynecology, State Hospital Hall, Hall, Austria
[9]Department of Visceral Surgery, State Hospital Hall, Hall, Austria
[10]Department of Obstetrics and Gynecology, County Hospital Schwaz, Schwaz, Austria
[11]Department of Internal Medicine, County Hospital St Johann, St Johann, Austria
[12]Departments of Health Policy & Management and Epidemiology, Center for Health Decision Science, Harvard T.H. Chan School of Public Health, Boston, MA
[13]Institute for Technology Assessment and Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA
[14]Division of Genetic Epidemiology, Department of Medical Genetics, Molecular and Clinical Pharmacology, Medical University of Innsbruck, Innsbruck, Austria
[15]Private Practice for Oral and Maxillofacial Surgery, Salzburg, Austria

## CORRESPONDING AUTHOR

Christine Brunner, MD; e-mail: c.brunner@tirol-kliniken.at.



## PRIOR PRESENTATION

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.24.00171.

## AUTHOR CONTRIBUTIONS

**Conception and design:** Christine Brunner, Christian Marth, Daniel Egle, Florentina Baumgart, Benjamin Walch, Birgit Volgger, Michael Hubalek, Uwe Siebert, Emanuel Bruckmoser, Johannes Laimer
**Administrative support:** Benjamin Walch
**Provision of study materials or patients:** Benjamin Walch, August Zabernigg, Birgit Volgger, Maria Castellan, Alice Markl
**Collection and assembly of data:** Christine Brunner, Daniel Egle, Florentina Baumgart, Miriam Emmelheinz, Benjamin Walch, Johanna Lercher, Claudia Iannetti, Ewald Wöll, Agnes Pechlaner, August Zabernigg, Birgit Volgger, Maria Castellan, Oliver Tibor Andraschofsky, Alice Markl, Michael Hubalek, Michael Schnallinger, Sebastian Schönherr, Lukas Forer, Johannes Laimer
**Data analysis and interpretation:** Christine Brunner, Marjan Arvandi, Christian Marth, Daniel Egle, Miriam Emmelheinz, Benjamin Walch, Birgit Volgger, Michael Hubalek, Michael Schnallinger, Sibylle Puntscher, Uwe Siebert, Emanuel Bruckmoser, Johannes Laimer
**Manuscript writing:** All authors
**Final approval of manuscript:** All authors
**Accountable for all aspects of the work:** All authors



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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Incidence of Medication-Related Osteonecrosis of the Jaw in Patients With Breast Cancer During a 20-Year Follow-Up: A Population-Based Multicenter Retrospective Study**

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**Christine Brunner**
**Employment:** Roche
**Honoraria:** Amgen, Daiichi Sankyo/Astra Zeneca, Roche, Novartis Institutes for BioMedical Research
**Consulting or Advisory Role:** Roche
**Speakers' Bureau:** AstraZeneca
**Travel, Accommodations, Expenses:** Daiichi Sankyo/Astra Zeneca, Amgen, Roche

**Christian Marth**
**Honoraria:** AstraZeneca, GlaxoSmithKline, MSD
**Consulting or Advisory Role:** MSD, GlaxoSmithKline, AbbVie
**Travel, Accommodations, Expenses:** Roche, AstraZeneca

**Daniel Egle**
**Honoraria:** AstraZeneca, Gilead Sciences, Daiichi Sankyo Europe GmbH, Pfizer, Roche/Genentech, Novartis, Lilly, Sirius Medical
**Consulting or Advisory Role:** AstraZeneca, Daiichi Sankyo Europe GmbH, Gilead Sciences, Novartis, Lilly
**Research Funding:** Sirius Medical (Inst)
**Travel, Accommodations, Expenses:** Daiichi Sankyo Europe GmbH, Pfizer

**Florentina Baumgart**
**Travel, Accommodations, Expenses:** Sandoz

**Miriam Emmelheinz**
**Travel, Accommodations, Expenses:** Teva, Sandoz

**Claudia Iannetti**
**Honoraria:** Lilly

**Ewald Wöll**
**Consulting or Advisory Role:** Amgen Astellas BioPharma

**August Zabernigg**
**Honoraria:** Roche, BMS GmbH & Co. KG, AstraZeneca, Takeda, Lilly
**Consulting or Advisory Role:** Amgen, Takeda
**Travel, Accommodations, Expenses:** Lilly, OPSI

**Birgit Volgger**
**Consulting or Advisory Role:** Novartis, Gilead Sciences, GlaxoSmithKline, Pfizer, AstraZeneca, Eisai, MSD
**Travel, Accommodations, Expenses:** MSD, Pfizer

**Maria Castellan**
**Honoraria:** Roche Novartis, Sanova, Daiichi Sankyo, Seagen, Gilead, Lilly, Pfizer
**Consulting or Advisory Role:** Novartis, Lilly
**Travel, Accommodations, Expenses:** Pfizer, Roche, Novartis, Daiichi Sankyo, MSD, Lilly

**Michael Schnallinger**
**Honoraria:** Janssen
**Consulting or Advisory Role:** Novartis, Janssen, Amgen, Takeda
**Travel, Accommodations, Expenses:** Roche, Novartis

**Lukas Forer**
**Honoraria:** Novartis

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## APPENDIX

**TABLE A1.** Details on Dental Disease

| Cause of MRONJ | Patients, N = 56, No. (%) |
|---|---|
| Peri-implantitis | 2 (3.6) |
| Tooth removal | 23 (41.1) |
| Denture pressure points | 13 (23.2) |
| Periodontitis | 1 (1.8) |
| Deep caries | 2 (3.6) |
| Chronical apical periodontitis | 4 (7.1) |
| Unknown | 11 (19.6) |

Abbreviation: MRONJ, medication-related osteonecrosis of the jaw.

**TABLE A2.** Sensitivity Analysis

| | Logistic Regression | | Cox Proportional Hazards | |
|---|---|---|---|---|
| | Odds Ratio (95% CI) | | Hazard Ratio (95% CI) | |
| Model | Only Denosumab | Denosumab After Bisphosphonates | Only Denosumab | Denosumab After Bisphosphonates |
| Crude analysis | 4.7 (2.0 to 10.7) | 6.9 (2.7 to 17.5) | 8.6 (3.5 to 21.4) | 1.2 (0.5 to 2.9) |
| Main analysis | 18.8 (2.4 to 145.2) | 17.8 (2.2 to 147.5) | 60.4 (6.4 to 577.6) | 5.7 (0.7 to 48.9) |
| Sensitivity analysis 1 | 6.7 (1.9 to 23.0) | 7.4 (2.0 to 27.9) | 14.5 (3.7 to 56.1) | 1.8 (0.5 to 6.7) |
| Sensitivity analysis 2 | 6.0 (1.7 to 20.5) | 7.5 (2.0 to 28.1) | 13.4(3.5 to 50.9) | 1.8 (0.5 to 6.6) |
| Sensitivity analysis 3 | 4.8 (2.1 to 11.0) | 6.4 (2.5 to 16.2) | 9.0 (3.6 to 22.9) | 1.1 (0.5 to 2.8) |
| Sensitivity analysis 4 | 4.8 (2.1 to 11.1) | 6.3 (2.5 to 16.1) | 8.7 (3.5 to 21.6) | 1.1 (0.4 to 2.8) |

NOTE. Crude analysis: univariate analysis without adjustment; main analysis: adjusted for all predictors of treatment with a significance level below 0.2 (age at diagnosis, menopausal status, primary or secondary metastasis, osteoporosis, use of cortisone, and HER2-positive, hormone receptor–positive, and triple-negative breast cancer); sensitivity analysis 1: adjusted for all variables with a significance level below 0.05 or without missing values (age at diagnosis, menopausal status, primary or secondary metastasis, osteoporosis, use of cortisone, and HER2-positive and triple-negative breast cancer); sensitivity analysis 2: adjusted for variables with a significance level below 0.05 (age at diagnosis, menopausal status, osteoporosis, use of cortisone, and triple-negative breast cancer); sensitivity analysis 3: adjusted for only variables with a significance level below 0.2 that did not have missing values (age at diagnosis and primary or secondary metastasis); sensitivity analysis 4: adjusted for only age as the most important potential baseline confounder.
Abbreviation: HER2, human epidermal growth factor receptor 2.