



Original Research

Treatment and pattern of bone metastases in 1094 patients with advanced breast cancer – Results from the prospective German Tumour Registry Breast Cancer cohort study



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Abstract A high proportion of patients with breast cancer develop bone metastases, yet data on routine treatment with bone-targeted agents (BTA) are rare. We report real-life outcome data of patients with breast cancer metastasised to the bone treated by office-based oncologists in Germany.

The ongoing, prospective, multicentre, population-based cohort study Tumour Registry Breast Cancer (TMK) was started in 2007 in 140 centres across Germany.

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Bone metastasis;
Diphosphonates;
Denosumab

This interim analysis of 1094 patients with bone metastases revealed differences among the tumour subtypes: at start of first-line therapy, 36% of the patients with hormone receptor (HR)-positive and only 20% of the patients with HR-negative tumours presented with bone-only metastasis. The majority of patients with bone metastases (89%, $n = 976$) received BTA therapy. In 2014–2015, 37% of the patients received the bisphosphonate zoledronic acid and 36% the antibody denosumab. Median duration of BTA therapy was 20 months (interquartile range 31.5 months), starting a median of 3 weeks after diagnosis of bone metastases, and ending a median of 7 weeks before death. The median overall survival (OS) also varied among the types of metastasis at start of first-line therapy ranging from 54 months (95% confidence interval [CI] 37.6–70.8), 38 months (95% CI 29.4–44.2) to 28 months (95% CI 24.2–31.0) for patients with bone-only metastases, non-visceral with or without bone metastases and visceral with or without bone metastases respectively.

We show that choice and duration of BTA therapies are in conformity with guidelines applicable in Germany. To our knowledge, this is the first presentation of data on incidence, metastatic pattern, treatment and survival of patients with bone metastases in routine practice.

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1. Introduction

Breast cancer is the leading cause of cancer deaths in women, with half a million deaths worldwide every year [1]. More than 90% of these deaths are caused by metastasis [2]. Despite recent advances, treatment of advanced breast cancer remains palliative, and the survival times for the patients vary greatly. Breast cancer displays a distinct metastatic pattern with the skeleton as predominant metastatic site [2,3]. About 65–75% of the patients with metastatic breast cancer develop bone metastases [4,5]. However, these numbers stem from data arising out of autopsies in the 1970s, and current data on the pattern and incidence of bone metastases in advanced breast cancer on population level are limited [6–8]. Prognosis for patients with distant metastasis to the bone is more favourable than for those with visceral or multiple metastases [9–11]. Treatment of bone metastases is generally palliative, aiming at reducing the symptoms, improving quality of life and possibly prolonging survival. Several bone-targeted agents (BTAs) are approved and are currently considered the standard of care [12–14]. The main types of bone-targeted agents are bisphosphonates and the RANK-ligand (RANKL) inhibitor denosumab. Bisphosphonates induce apoptosis of osteoclasts and thus inhibit bone resorption [15] and reduce the skeletal morbidity rate [16]. The synthetic antibody denosumab specifically inhibits the maturation of osteoclasts and was shown to be superior to zoledronic acid in reducing skeletal-related events (SREs) such as surgery or radiotherapy to the bone, pathological fracture, spinal cord compression or hypercalcaemia [17]. Efficacy of these BTAs in treatment of bone metastases has been established in randomised controlled trials (RCTs) [16,18]. However, the demographic and medical characteristics of the general population often differ from patients enrolled in clinical

trials. There are only few data on the use of BTAs in routine care, and existing data are often limited by retrospective collection [6,19,20].

In this article, we present data on patients with breast cancer metastasised to the bone. Data are derived from a prospective clinical cohort study covering patients treated by office-based medical oncologists in Germany. We show the metastatic pattern of 1094 patients at start of their first-line therapy as well as during the course of the disease. Furthermore, we present details on the BTA therapy and show that the overall survival (OS) varies among patients with differing metastatic pattern.

2. Patients and methods

2.1. Data source

The Tumour Registry Breast Cancer (TMK) is an ongoing, open, longitudinal, multicentre, observational, prospective cohort study which started in 2007. The study was approved by the responsible ethics committee and is registered at ClinicalTrials.gov (TMK registry, NCT01351584). The TMK methodology has previously been described in detail [21].

Eligible patients for the present analysis were women aged ≥ 18 years with advanced breast cancer at the start of their first palliative systemic antineoplastic treatment. Administration of each BTA is documented with the date of first and last dose, dosage and route of administration. Data on the location of metastases are documented at inclusion and then updated upon any change, but at least every 6 months. In order to collect representative data for routine treatment in Germany, a large number of outpatient-centres for medical oncology located all over Germany take part in the TMK. At the time of this analysis, 140 such study sites were actively participating.

2.2. Cohort definition

At data cut for this interim analysis (31st October 2015), 1801 patients of the TMK received systemic first-line palliative therapy and had records on the presence of metastases at start of treatment (12 weeks before until 8 weeks after start of therapy, Fig. 1). Until the time of data cut for this interim analysis, bone metastases had been documented for 1104 patients (892 patients had bone metastases at start of first-line treatment and 212 patients developed bone metastases during the course of the disease). We focussed on 1094 patients with documentation on BTA therapy (Answer yes/no to the question “BTA therapy received?”). The substance-specific analyses are based on the number of patients with data on the BTA used (n = 976). OS is presented from start of first-line therapy for those patients with bone metastases and documentation on BTA therapy prospectively enrolled until 31st October 2013 (n = 678) to ensure a follow-up period of at least 2 years for all patients. At the time of this analysis, the documentation had been finished for 812 patients, 570 patients had died. Median observation time was 30 months.

2.3. Statistical analysis

OS is defined as the interval between start of first-line therapy and the date of death from any cause. Patients alive or lost to follow-up at data cut were censored at last contact. The BTA treatment duration was calculated using a Kaplan–Meier estimate for all patients with documented starting date of the initial BTA therapy. Patients alive, who had not completed BTA treatment at the time of data cut for this analysis, were censored at the last documented date of patient contact. Median follow-up was defined as time from informed consent to last documented date of patient contact. Kaplan–Meier estimates for OS and treatment duration were calculated using SAS for Windows Version 9.4 with 95% confidence limits for the survival estimates. All other analyses were performed using IBM SPSS Statistics version 19.0.

3. Results

3.1. Patient and tumour characteristics

The demographic and clinical characteristics of patients with breast cancer metastasised to the bone are shown in Table 1. Median age was 62.8 years (range 24.5–87.8), 73% were HR-positive, 24% human epidermal growth factor receptor 2 (HER2)-positive and 9% triple negative i.e. oestrogen receptor (ER)-negative, progesterone receptor (PR)-negative, as well as HER2-negative. 60% of the patients reported at least one concomitant disease, yet 85% had a Charlson comorbidity index (CCI)

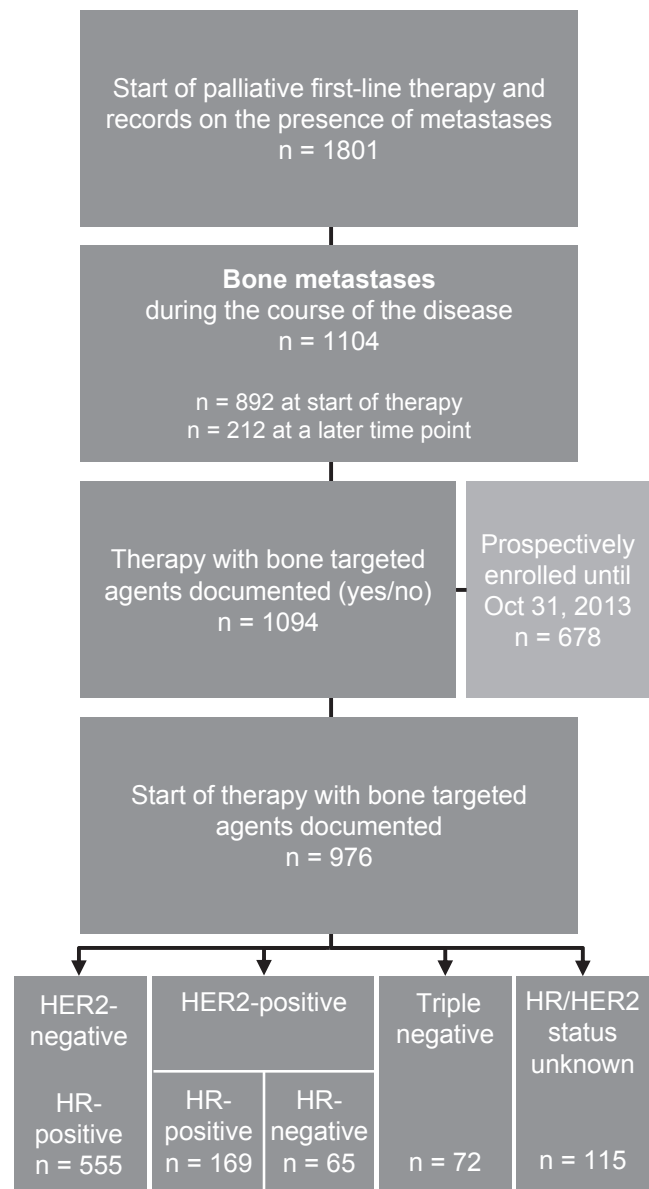


Fig. 1. Cohort definition. Number of patients enrolled in the TMK with palliative treatment intention. Only patients with documented metastases in the course of their disease were included in this analysis. Abbreviations: HR, hormone receptor; HER2, human epidermal growth factor receptor 2; triple negative: negative for HR and HER2.

of 0, which indicates that most patients were in good general condition at start of treatment. Overall, 89% of the patients received BTA therapy.

3.2. Metastatic pattern

The metastatic pattern for all patients with bone metastases and information on BTA therapy (n = 1094) is shown in Fig. 2. The majority of these patients (81%) presented with initial bone metastasis. Patients with

Table 1
Patient and tumour characteristics.

Characteristic	BTA therapy (n = 976)	No BTA therapy (n = 118)	All patients (n = 1094)
Age, years (median, range) ^a	62.9 (24.5–87.8)	61.3 (29.4–84.6)	62.8 (24.5–87.8)
BMI, n (mean ± SD) ^b	901 (26.8 ± 5.1)	113 (25.9 ± 5.5)	1014 (26.7 ± 5.2)
Receptor status at primary diagnosis			
HR-positive, HER2-negative	555 (56.9%)	52 (44.1%)	607 (55.5%)
HR-positive, HER2-positive	169 (17.3%)	21 (17.8%)	190 (17.4%)
HR-negative, HER2-positive	65 (6.7%)	10 (8.5%)	75 (6.9%)
Triple negative	72 (7.4%)	22 (18.6%)	94 (8.6%)
Unknown	115 (11.8%)	13 (11.0%)	128 (11.7%)
Palliative first-line therapy			
Chemotherapy	522 (53.5%)	97 (82.2%)	619 (56.6%)
Endocrine therapy	454 (46.5%)	21 (17.8%)	475 (43.4%)
Patients with at least one comorbidity ^{b,c}	551 (56.5%)	69 (58.5%)	620 (56.7%)
CCI 0 ^d	782 (80.1%)	94 (79.7%)	876 (80.1%)
CCI 1 ^d	42 (4.3%)	7 (5.9%)	49 (4.5%)
CCI 2 ^d	68 (7.0%)	6 (5.1%)	74 (6.8%)
CCI 3+ ^d	31 (3.2%)	4 (3.4%)	35 (3.2%)
Unknown	52 (5.3%)	7 (5.9%)	59 (5.4%)
Metastasis at primary diagnosis			
No (M0)	544 (55.7%)	74 (62.7%)	618 (56.5%)
Yes (M1)	315 (32.3%)	30 (25.4%)	345 (31.5%)
MX ^e	109 (11.2%)	12 (10.2%)	121 (11.1%)
Missing	8 (0.8%)	2 (1.7%)	10 (0.9%)
Menopausal status ^b			
Premenopausal	137 (14.0%)	11 (9.3%)	148 (13.5%)
Perimenopausal	27 (2.8%)	7 (5.9%)	34 (3.1%)
Postmenopausal	635 (65.1%)	82 (69.5%)	717 (65.5%)
Unknown	177 (18.1%)	18 (15.3%)	195 (17.8%)

Abbreviations: BMI, body mass index in kg/m²; BTA, bone-targeted agent; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; SD, standard deviation.

^a At start of palliative first-line therapy.

^b At enrolment.

^c Comorbidities according to Charlson or additional concomitant diseases.

^d Charlson Comorbidity Index (CCI) according to Quan *et al.* [22].

^e MX, presence of distant metastasis was not evaluated or was unknown at the time of primary diagnosis.

different tumour subtypes showed a different metastatic pattern when followed from initial diagnosis until data cut at 31st October 2015. At start of first-line therapy, HR-positive patients more often had bone-only metastases (37% HER2-negative/HR-positive and 35% HER2-positive/HR-positive) than HR-negative patients (20% HER2-positive/HR-negative and 19% triple negative). During the course of the disease, the number of patients with bone-only metastases decreased to a range of 17–22% in HR-positive and to a range of 9–12% in HR-negative patients (Fig. 2). Consequently, the number of patients with multiple metastatic sites increased from 12% to 31% in the total patient sample. The proportion of patients with bone and additional visceral metastases increased from 24% to 38% whereas the proportion of patients with bone and non-visceral metastases was stable at 10% in the total patient sample (Fig. 2).

Taking a closer look at the metastatic pattern of all patients, the frequencies of initial metastatic sites as well as the respective subsequent sites are shown in Fig. 3, indicating advanced tumour growth from the skeleton

to both visceral and non-visceral sites. The tumour had progressed to subsequent visceral sites in 12% of the patients, to non-visceral sites in 6% and to both visceral and non-visceral sites in 11% of the patients with bone metastases at start of first-line therapy, at the time of data cut. The number of patients with bone-only metastasis had decreased from 35.3% at enrolment to 20.4% in the course of the disease. The median observation time was 30 months for the total patient sample. The tables with these data, split up according to the tumour subtypes, are shown in the supplementary material (Table S1).

Of all 1094 patients with bone metastases, 218 (20%) underwent palliative surgery and 62 (6%) received surgery to the bone. 569 (52%) of the patients received palliative radiotherapy, 390 (36%) radiotherapy of the bones. Two-thirds of these radiotherapies of the bones (262, 67%) and almost half of the surgeries to the bone (28, 45%) were conducted after start of BTA therapy. Data on other SREs (fractures, spinal cord compression and hypercalcaemia) were not recorded.

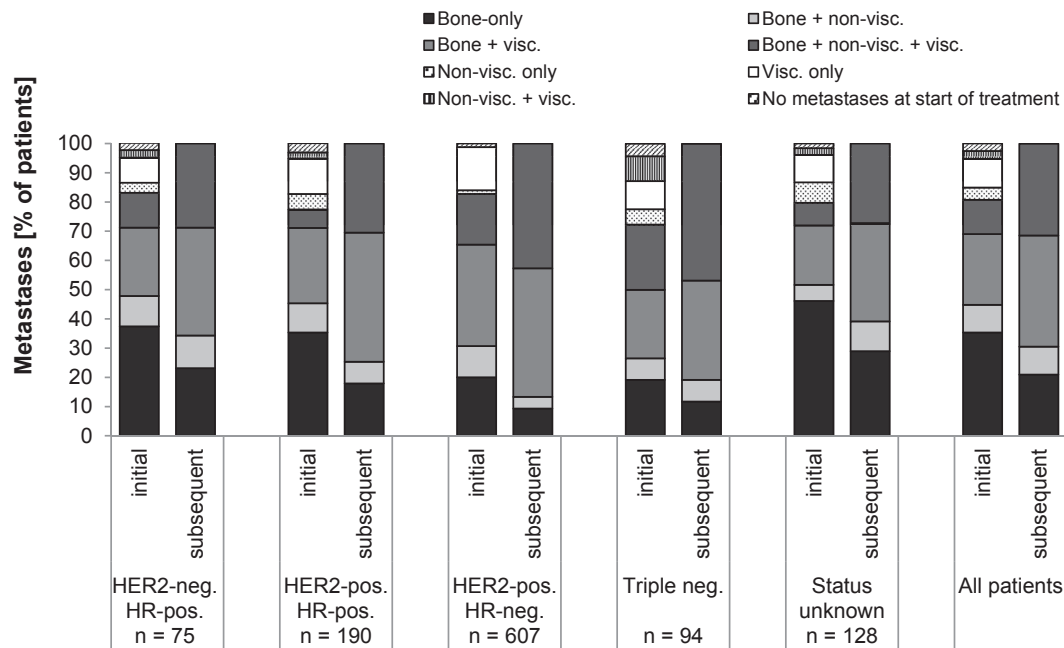


Fig. 2. **Metastatic pattern according to the tumour subtypes.** Metastatic pattern split up according to the tumour subtypes, showing the distribution of metastases both at the beginning (initial) and at data cut (subsequent). In total, data of 1094 patients were analysed. Non-visceral: skin and lymph node metastases. A small proportion of patients (28, 2.6%) presenting with locally advanced, inoperable disease at start of first-line treatment had no metastases at the initial assessment, yet developed bone metastases in the course of the disease. **Abbreviations:** HR, hormone receptor; HER2, human epidermal growth factor receptor 2; neg., negative; pos., positive; non-visc., non-visceral; visc., visceral.

3.3. Treatment rate and switches in treatment

In total, 89% of the patients with bone metastases received a BTA therapy. The four main types of BTAs administered were the bisphosphonates zoledronic acid, pamidronate, ibandronate and the antibody denosumab (Fig. 4A). Since the approval of denosumab for skeletal metastases in July 2011, the proportion of patients receiving this agent has increased markedly, reaching 36.2% in 2014–2015, drawing level with zoledronic acid (37.2% in 2014–2015).

So far, about one-fourth of the patients have switched within BTA therapy at least once during the course of the disease (Fig. 4B). In line with the approval of denosumab 4 years after start of the TMK, a higher proportion of patients received bisphosphonate treatment. Some 10% of the patients initially receiving a bisphosphonate have switched to another type of bisphosphonate during the course of the disease while 9% have switched to denosumab until data cut. The patients initially receiving denosumab are mostly still on treatment (55%) and 5% have switched to a bisphosphonate (Fig. 4B).

3.4. Treatment duration

Patients in the TMK started their therapy with BTAs a median of 3 weeks (22 days, interquartile range [IQR] 42 days) after diagnosis of bone metastases (Fig. 5).

Median duration of the initial BTA therapy was 19.9 months (IQR 31.5 months, Kaplan–Meier estimate). Median time from end of BTA therapy until death was 7 weeks (47 days, IQR 80 days) for the 452 patients (46%) that had received BTA and had died until data cut. Thus, the majority of patients received their BTA therapy throughout the course of the disease. The cause of death was documented for 96% of the patients with 81% of them dying due to their tumour disease.

3.5. Overall survival

Only patients prospectively enrolled until 31st October 2013 were included in this analysis to ensure a sufficient follow-up time. OS varies among patients with different metastatic patterns at start of first-line therapy (Fig. 6). Patients with bone-only metastases at start of first-line therapy had a median OS of 54 months (95% CI 37.6–70.8) compared to 37 months for patients with non-visceral with or without bone metastases (95% CI 29.4–44.2) and 28 months for patients with visceral with or without bone metastases (95% CI 24.2–31.0). Of note, patients with visceral metastases at the start of first-line therapy more often had triple-negative tumours, while patients with bone-only metastases more often had HR-positive tumours (Fig. 2). In terms of age and percentage of patients with comorbidities patients in these three subgroups were comparable. Furthermore, only 46% of the patients with bone-only metastasis had

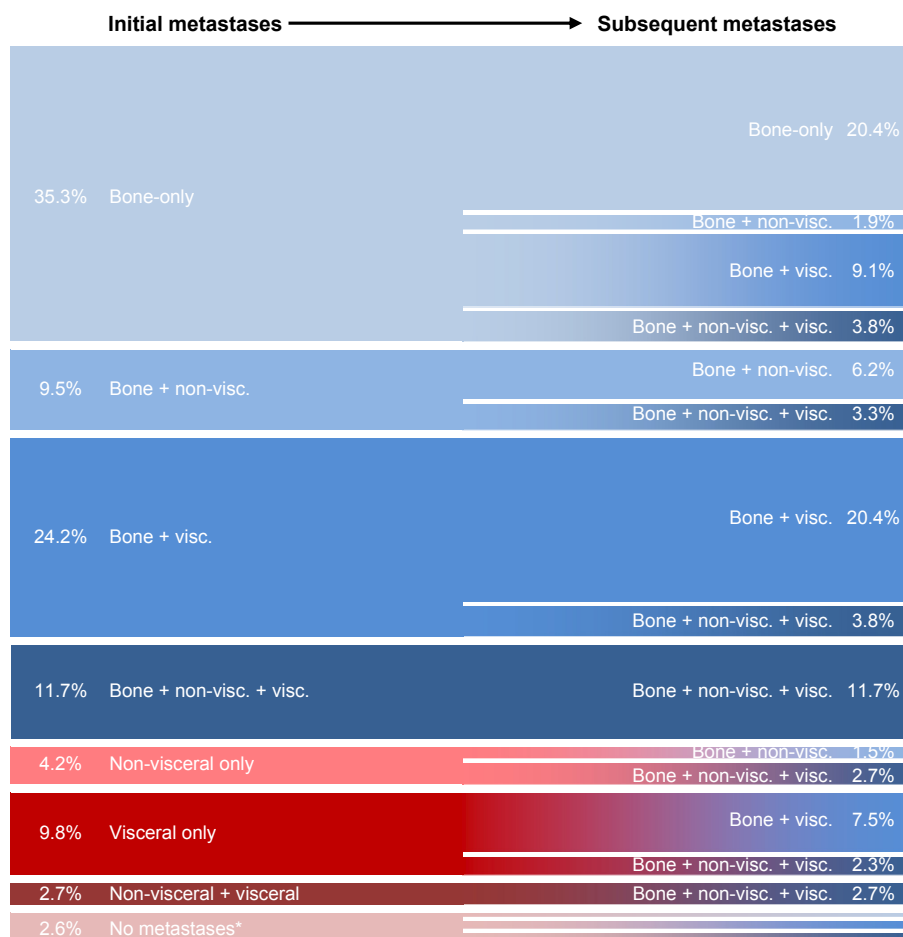


Fig. 3. **Pattern of metastases throughout the course of the disease.** The sequential metastatic pattern for all patients with bone metastases (n = 1094). The frequencies of the different metastases both at the beginning (initial) and at data cut (subsequent) are indicated. * A small proportion of patients (28, 2.6%) presenting with locally advanced, inoperable disease at start of first-line treatment had no metastases at the initial assessment, yet developed bone metastases in the course of the disease: 0.5% developed bone-only, 1% bone with or without visceral and 1% bone with or without visceral with or without non-visceral metastases. Non-visceral: skin and lymph node metastases. The median observation time was 30 months. **Abbreviations:** neg., negative; pos., positive; non- visc., non-visceral; visc., visceral.

died at the time of this analysis; therefore their median survival estimate is still to be finally determined as also indicated by the broad 95% confidence interval.

4. Discussion

Bone metastases affect a large proportion of patients with advanced breast cancer and have a profound impact on their mobility and quality of life. While there are multiple clinical trials on BTA therapy in small and distinct subsets of this population, there is no such information for routine treatment. To our knowledge, this is the first dataset covering treatment and survival in a real-world population. We show that the metastatic pattern at the start of first-line treatment correlates with the tumour subtype and overall survival. As much as 89% of the patients received BTA therapy, with most of them receiving either zoledronic acid or denosumab. The median treatment duration was 20 months.

The limitation of this study is its observational nature, which does not allow causal conclusions. The exclusive enrolment of patients receiving systemic first-line therapy limits generalisations about choice of BTA treatment for all patients not receiving systemic treatment. Strengths of this study are the prospective data collection and the participation of office-based medical oncologists all over Germany, recruiting a large representative study population for this treatment setting.

Despite ongoing research, systematic data on the incidence and treatment of breast cancer metastasised to the bone are rare. In this study, 63% of the patients with advanced breast cancer had developed bone metastases at the time of data cut, corresponding well to the proportion of 65–75% reported in the literature [4,5]. The metastatic pattern seems to be closely associated with the tumour subtype. While bone, lung, liver, brain and the distant lymph nodes are the main target organs [2], the HR-positive tumours have a predisposition to

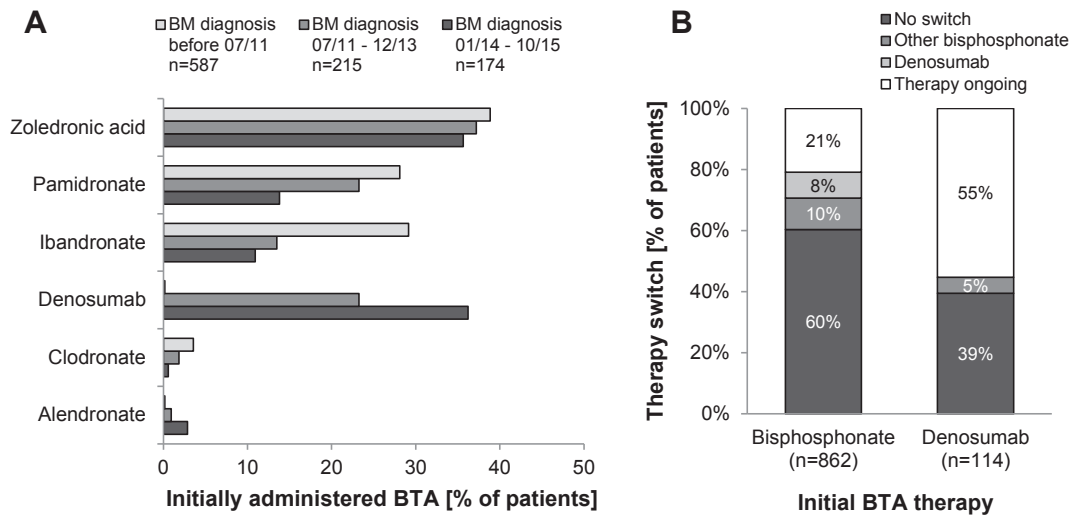


Fig. 4. **Treatment rate and switches of 976 patients.** (A) Shown is the proportion of patients initially receiving the different bone-targeted agents (BTA), split by the date of diagnosis of bone metastases since 2007. The subdivision by time of diagnosis clearly shows the effect of the approval of denosumab in July 2011. (B) Proportion of patients receiving BTA therapy. Both the ongoing therapies as well as the switches from initial bisphosphonate or denosumab therapy are shown. Patients with “no switch” had completed their BTA treatment without a change in BTA. **Abbreviations:** BM, bone metastases; BTA, bone-targeted agent.

metastasise to bone, rather than to the visceral organs [10,11,23]. These findings are mirrored in our analysis, with 35–37% of bone-only metastases at the start of first-line treatment originating from HR-positive tumours, compared to 19–20% of HR-negative tumours. Taken together, 35% of the whole cohort reported bone-only metastasis at the start of treatment, which is consistent with the literature naming a proportion of 17–37% [11,24]. In contrast, HER2-positive tumours are more likely to metastasise to the brain during the

course of disease, with an incidence of 25–34% [2,25,26]. Consistent with these results, the frequency of brain metastases in the HER2-positive setting was 31% during the course of disease in our cohort (data on file). Triple negative tumours are associated with the worst prognosis, mainly attributed to a high rate of early relapse. Their metastatic pattern most often affects the lung and the lymph nodes [23,25], which is consistent with our cohort showing a higher propensity for metastasis to the lung during the course of disease (39%, data on file).

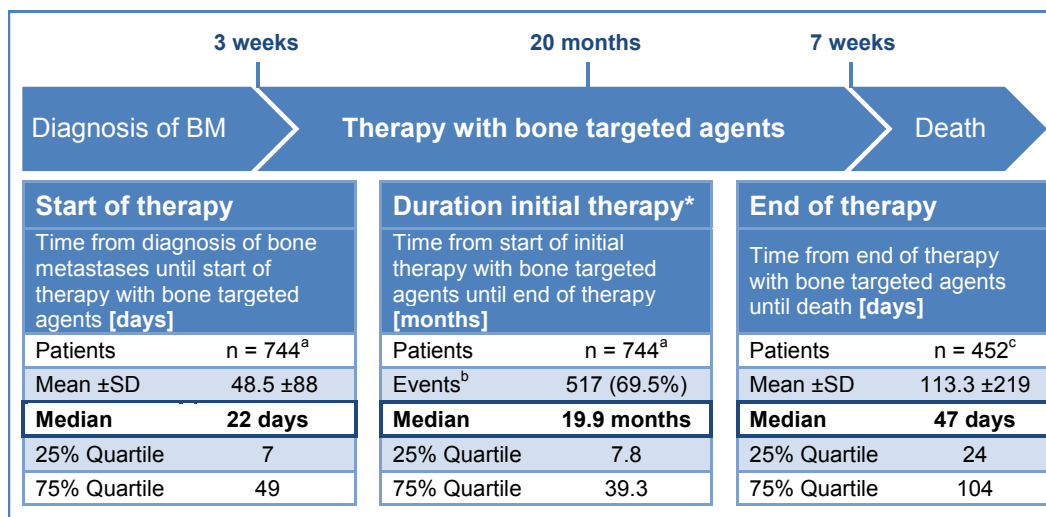


Fig. 5. **Treatment duration.** The time bar visualises the median times of treatment duration. The table indicates the number of patients included in the respective analysis. ^aNumber of patients with documented start of BTA therapy isochronal or after diagnosis of bone metastases. Patients with missing data regarding one of these parameters or patients who had started BTA therapy before diagnosis of bone metastases were excluded from this analysis. *Kaplan–Meier estimate. ^bNumber of patients with documented end of therapy or date of death. ^cNumber of patients whose last BTA therapy was finished and who have died. **Abbreviations:** BM, bone metastases; SD, standard deviation.

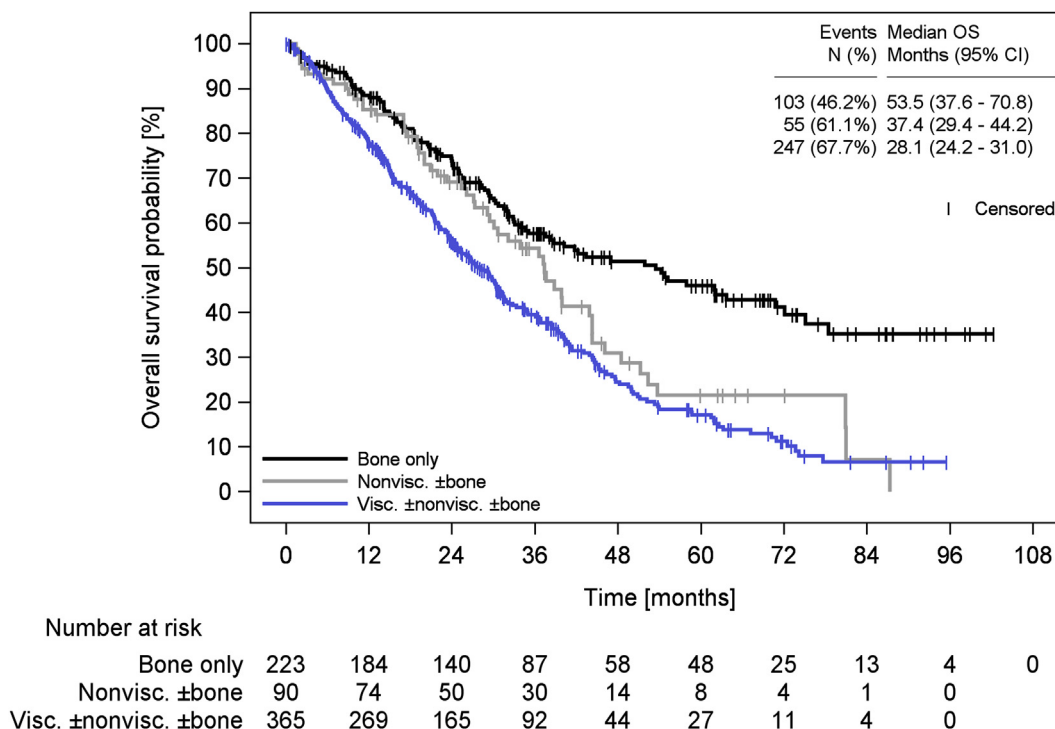


Fig. 6. **Overall survival.** Overall survival of patients with bone metastases from breast cancer. All patients starting first-line therapy until October 31, 2013 ($n = 678$) were included in this analysis (see Fig. 1). Bone-only metastasis, $n = 223$; non-visceral with or without bone metastasis, $n = 90$; visceral with or without non-visceral with or without bone metastasis, $n = 365$. **Abbreviations:** non-visc., non-visceral: skin and lymph node metastases; visc., visceral; CI, confidence interval.

Research is ongoing to explore factors impacting metastatic tumour spread in order to develop novel therapeutic targets.

Regarding the treatment of bone metastases with BTAs, the current guidelines recommend bisphosphonates or denosumab in combination with oral calcium and vitamin D supplementation as palliative care measures [27–30]. A SEER database evaluation from 1995 to 2004 showed that the use of bisphosphonates increased considerably over time, yet appeared to be underused especially in elderly patients with metastatic breast cancer [31]. This undertreatment was not observed in our cohort: some 88% of the patients aged ≥ 75 were treated with BTAs, compared to 90% of the younger patients. In total, 89% of the patients with bone metastases received BTA therapy in this study. This number is in line with the three population-based surveys available so far: Kuchuk *et al.* reported 88% of 176 patients, Canada 2008–2012, 86% receiving pamidronate [6]; Murphy *et al.* indicated 93% of 65 patients, Canada 2008–2010, 86% receiving pamidronate [20] and Arican *et al.* documented 96% of 1.026 patients, Turkey 2010–2011, 58% receiving ibandronate [19]. While pamidronate prevailed in these studies, zoledronic acid was the main bisphosphonate used in our cohort from 2007 to 2014 (37%). This reflects current guideline recommendations based on clinical trials showing that zoledronic acid is superior to pamidronate for the

treatment of bone metastases [32]. Since its approval in 2011, the RANKL-antibody denosumab [33], gained on zoledronic acid and was applied to 36% of the patients starting first-line therapy in 2014–2015. In our study cohort, BTA treatment was continued over a median of 20 months and was given until a median of 7 weeks before death in those patients that had died.

5. Conclusions

Treatment of patients with breast cancer metastasised to the bone in German routine practice conforms to clinical guidelines, with the majority of patients receiving BTA therapies throughout the course of their disease. The metastatic pattern and overall survival varied among patients with different tumour subtypes. However, despite recent advances in treatment, there is still much to be done in order to effectively prevent and treat bone metastases.

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Conflict of interest statement

JS, AK, VP, LS, AF and MJ declare no conflict of interest concerning the topic of this publication. HT and NM have received honoraria by Roche, Novartis, Celgene and Amgen for talks and attendance of conferences. TF has received honoraria by Novartis and AstraZeneca for talks and attendance of conferences.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.ejca.2017.03.031>.

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