



Research Paper

Real-world patient-reported outcomes of breast cancer or prostate cancer patients receiving antiresorptive therapy for bone metastases: Final results of the PROBone registry study



Andreas Jakob^a, Mark-Oliver Zahn^b, Arnd Nusch^c, Thorsten Werner^d, Roland Schnell^e, Melanie Frank^f, Nicole Hamm^f, Klaus-Ulrich Däßler^g, Christoph Losem^h, Manfred Welslauⁱ, Petra Hoevel^j, Karin Potthoff^{f,*}

^aTumor Center Aarau, Hirslanden Medical Center, Switzerland

^bOncology Practice Goslar, Goslar, Germany

^cPractice for Hematology and Internal Oncology, Ratingen, Germany

^dUrology Praxis Herzberg, Herzberg am Harz, Germany

^ePractice for Internal Oncology and Hematology, Frechen, Germany

^fiOMEDICO, Freiburg, Germany

^gOncology Practice, Freital, Germany

^hMedical Care Center for Oncology and Hematology, Neuss, Germany

ⁱMedical Care Center at Hospital Aschaffenburg GmbH, Aschaffenburg, Germany

^jMedical Care Center at General Hospital Celle, Celle, Germany

ARTICLE INFO

Article history:

Received 6 October 2021

Revised 15 February 2022

Accepted 27 February 2022

Available online 3 March 2022

Keywords:

Bone metastases

Bone pain

Antiresorptive treatment

Bone-targeted agents

Quality of life

ABSTRACT

Background: In breast cancer and prostate cancer patients, bone metastases (BM) present the main cause of morbidity and often cause debilitating pain, impaired functioning and subsequent deterioration of quality of life (QoL). The management of BM is still challenging. Maintenance or improvement in QoL is the main goal of treatment. Antiresorptive treatment, such as denosumab and bisphosphonates, can help to reduce the frequency of skeletal complications, to control bone pain and potentially to improve QoL. The optimal time point for initiation of antiresorptive therapy is still discussed controversially. In patients with BM, bone pain can be used as a surrogate measure of QoL. However, limited data exist on health-related QoL in patients with BM under antiresorptive treatment. The PROBone registry study evaluated complaints and limitations caused by BM of breast and prostate cancer patients using patient-reported outcomes (PROs) in real-world in Germany.

Methods: Between 2014 and 2019, 500 patients with histological confirmation of advanced breast or prostate cancer, diagnosed with BM at start of their first antiresorptive therapy were prospectively enrolled in 65 outpatient-centers specialized in medical oncology across Germany. Changes of QoL were assessed monthly from baseline until a maximum of 12 months using the validated pain score Functional Assessment of Cancer Therapy Quality of Life Measurement in patients with bone pain (FACT-BP) supplemented by questions on general pain and on the impact of time spent for treatment of illness on patients' daily activities. Statistical analysis was performed descriptively by relative and absolute frequencies.

Results: In total, 486 patients were eligible for final analysis, of these 310 were diagnosed with breast cancer and 176 with prostate cancer. Median age was 67 years for breast cancer and 76 years for prostate cancer patients. 79.7% of breast cancer and 59.7% of prostate patients started antiresorptive treatment within 3 months after diagnosis of BM. More than 75% of patients suffered from bone pain at study inclusion. In total 52% of breast cancer patients and 47.9% of prostate cancer patients reported to take pain medication during the observation period. In breast and prostate cancer patients an initial pain reduction after start of BTA was observed: General pain and bone pain levels as well as the median FACT-BP score showed a constant improvement over the first months and maintained stable at a constant level afterwards. Subgroup analysis showed that patients without pain at baseline reported distinctly better

Abbreviations: BM, Bone Metastases; BTA, Bone-targeted Agents; FACT-BP, Functional Assessment of Cancer Therapy – Bone Pain questionnaire; PRO, Patient-Reported Outcome; QoL, Quality of Life; RANK, Receptor Activator of Nuclear factor Kappa-B; SRE, Skeletal-Related Events; VAS, Visual Analogue Scale.

* Corresponding author.

E-mail address: manuscript@iomedico.com (K. Potthoff).

<https://doi.org/10.1016/j.jbo.2022.100420>

2212-1374/© 2022 iOMEDICO AG. Published by Elsevier GmbH.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

FACT-BP scores throughout the whole observation period than patients with pain at baseline. Looking at time-stress (M)-scores, younger breast cancer patients (<65 years) showed highest burden especially during the first months of treatment.

Conclusions: Our results indicate overall good adherence to current guideline recommendation, with most breast and prostate cancer patients starting antiresorptive therapy within the first 3 months after diagnosis of BM. This point gains even more importance as our data support current recommendations by ESMO guidelines as well as by German evidence-based S3-guidelines for diagnosis and treatment of breast and prostate cancer to initiate bone-targeted agents (BTA) as soon as BM are diagnosed, to keep pain levels at the lowest level possible, to minimize the debilitating effects of metastatic bone pain and maintain a good QoL. Bone pain management by an early use of BTA following BM diagnosis might improve patient care.

© 2022 iOMEDICO AG. Published by Elsevier GmbH. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Bone metastases (BM) represent one of the most common complications of advanced cancer. Up to 70% of patients with advanced breast cancer [1,2] and up to 90% of patients with advanced prostate cancer [3] are affected. Bone complications are known as skeletal-related events (SRE) and commonly defined as radiation therapy or surgery to bone, pathologic fractures, spinal cord compression, or tumor-induced hypercalcemia [4]. They may cause pain, impair physical activity and negatively impact patients' quality of life (QoL) [5]. Patients with BM frequently experience bone pain as well as pathologic fractures and spinal cord compression which results in debilitating cancer-related morbidity. Pain is often underreported due to the patients' reluctance to report pain [6]. Furthermore, in patients with bone metastases it often is inadequately assessed and under-treated. Bone-targeting agents (BTA), such as denosumab or bisphosphonates, may prevent skeletal-related complications and thus can relieve pain and improve the QoL of patients with BM [7]. Validated patient-reported outcome (PRO) instruments used to measure pain and impaired functioning in patients with BM are scarce and pain assessment is still challenging although required to assess patients' subjective experience and although being of crucial importance to optimize treatment and to reduce the burden of pain associated with metastatic bone disease [6].

Health care resources are substantially effected by the costs deriving from bone complications [8]. Considering the high number of patients developing BM and the fact that almost 50% of those experience at least one SRE [9], it is obvious that optimal treatment is an important concern.

Treatment of BM focuses on pain reduction and prevention or delay of onset of SRE, aiming at maintaining or improving QoL of patients and possibly prolong survival [10]. The main types of currently available BTA are bisphosphonates such as pamidronate and zoledronate and the Receptor Activator of Nuclear factor Kappa B (RANK)-Ligand inhibitor denosumab that act as inhibitors of bone resorption [9,11,12]. These agents became an international standard of care in treatment of breast and prostate cancer patients with BM [13]. Although BTA have been shown to reduce SRE and reduce pain levels in patients with moderate to severe pain [14,15], there is still an unmet need to optimize the use of BTA. Different treatment patterns, varying in time of commencing therapy, treatment duration and dose intensity are under discussion [16–18]. However starting treatment as soon as BM are diagnosed whether symptomatic or not is recommended in clinical guidelines [19]. Another important part of therapy of BM, that might help to increase patients QoL is symptomatic treatment like pain medication, radionuclide therapy and local surgery [19].

Due to the correlation of pain with reduced QoL, (bone) pain can be used as a surrogate measure of health-related QoL in patients

with BM [20,21]. However, also other factors like expenditure of time for treatment have an impact on QoL and have to be considered for a complete assessment of the patients' well-being.

There exist evidence suggesting that BTA might improve survival and reduce the risk of skeletal complications in patients with BM from breast and prostate cancer [22,23]. However, there is still a need for real-world data on the use of BTAs in patients with BM and the progress in patient well-being.

We conducted the PROBone registry study, gathering data on complaints and limitations specifically caused by BM in patients with advanced breast or prostate cancer diagnosed with BM, receiving antiresorptive therapy via patient-reported outcome measures. Data are derived from a non-selected patient cohort with BMs treated by office-based medical oncologists in Germany. The aim of PROBone was to gain new insight into patient reported pain and QoL during treatment with BTA in a real-world setting.

2. Patients and methods

2.1. Study design and patient eligibility

PROBone was a prospective multicenter, observational, epidemiologic patient-reported outcome (PRO) study conducted in Germany. The project plan as well as patient information and informed consent form, and patient questionnaire were reviewed and approved by the ethics committee. The study was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT02410044).

Eligible patients had histologically confirmed metastatic breast or prostate cancer, were diagnosed with BM and at start of their first antiresorptive therapy. Fluency in German and ability to fill out a questionnaire were also prerequisites for enrollment. Written informed consent was obtained from all patients. Enrollment was restricted to patients who completed their first questionnaire no longer than 7 days after start of their first antiresorptive treatment.

2.2. Data source

Patients' demographical and clinical data were transferred from medical records to a secure web-based electronic case report form (eCRF) by designated site staff. For quality assurance, data plausibility checks were performed, and queries were generated automatically by the eCRF software. Data were fully pseudonymized and all information collected in this study was treated strictly confidentially.

2.3. Questionnaires

The PROBone questionnaire (Appendix table A1) consisted of 23 items. It consisted of the validated pain score Functional Assess-

ment of Cancer Therapy Quality of Life Measurement in patients with bone pain (FACT-BP, 16 bone pain items) [24] supplemented by questions on general pain (visual analog scale (VAS), 1 general pain-item) [25], questions on pain management (2 items on taking of medication and effect of medication) and questions on the impact of time spent for treatment of illness on patients' daily activities (4 time-stress-items on daily routine, social life, ability to work and time burden).

Questionnaires were completed by the patients directly at the site. The questionnaires (PRO) were captured through project-specific configured tablets. Patients completed the questionnaires via touch screen directly at study site. Data were transmitted encoded and pseudonymized to a central database. In exceptional cases, paper questionnaires were used. Patients were requested to complete the first questionnaire at time of recruitment (referred to as baseline) and afterwards at every routine visit but maximal once per months for a time period of maximal twelve months.

2.4. Statistical analysis

Descriptive statistics were performed for analysis. The following prespecified subgroups were used: entity ('breast cancer' vs. 'prostate cancer'), age (breast cancer: subgroups '<65 years' vs. '≥65 years', prostate cancer: subgroups '<75 years' vs. '≥75 years'), metastases ('bone only' vs. 'bone and other organs'), bone pain at baseline ('no pain' vs. 'tolerable pain' vs. 'heavy pain'), and pain at baseline ('no pain' vs. 'pain' and 'no pain' vs. 'tolerable pain' vs. 'heavy pain').

Median time between diagnosis of bone metastasis and start of antiresorptive treatment was evaluated, while patients with documented therapy start before or later than 30 months after diagnosis of bone metastasis were considered as outlier and excluded from the analysis.

2.5. Patient-reported outcome

For analysis of questionnaires, time point analyses were performed on a monthly basis: Each questionnaire was assigned to a calculated month derived from the sum of days since first (baseline) questionnaire. Baseline is defined as month 0. Visit 1 to visit 12 are defined as calculated visit 1 to 12 months after baseline visit by calculating date of questionnaire minus the date of baseline questionnaire divided by 30.25. Decimals ≤ 0.4 were rounded down and decimals ≥ 0.5 were rounded up to the nearest whole value. Data of calculated months with values >12 were omitted from the analysis.

A questionnaire was considered evaluable for calculation of the FACT-BP-score when at least 8 items were completed and evaluable for the M-score when at least 3 items were available. For single item parameters, availability of the item was considered evaluable.

General pain-items were evaluated as single items. General pain was determined using item C1 (VAS). The item C1 asks for the presence of pain and respective intensity during the last seven days relative to assessment date. For stratification of patients by baseline pain, C1 (VAS) values were used. According to patients' reported data at baseline assessment, patients were categorized into two or three baseline pain occurrence groups, respectively. Groups 'no pain' and 'pain' which corresponds to C1 answer categories '0' and 'greater than 0', respectively, or groups 'no pain', 'tolerable pain' and 'heavy pain' which corresponds to C1 answer categories '0', '1-7' and '8-10', respectively.

The Scoring of the FACT-BP questionnaire was performed according to respective manual [26] and is referred to as FACT-BP score. The FACT-BP score ranges from 0 to 60. The higher the score, the better the bone pain related QoL.

Bone pain was determined using item BP1 of the FACT-BP questionnaire that asks for the presence of bone pain at assessment

date. For stratification by baseline bone pain also item BP1 was used. According to patients' reported data at baseline assessment, patients were categorized into three baseline bone pain groups 'no pain', 'tolerable pain' and 'heavy pain' which corresponds to BP1 answer categories '0', '1,2' and '3,4', respectively.

For the four time-stress-items, a sum score (M-Score) was calculated which represents the time-related distress due to time spent on cancer treatment in daily life. The M-score is the sum of the item categories (1-4), with higher M-scores reflecting higher time-stress levels or more negative impact on daily life.

Pearson correlation coefficients were calculated to evaluate the correlation between FACT-BP score and M-score at baseline and visit 12, i.e. the putative correlation between QoL and the impact of time spent on cancer treatment on daily life of patients with advanced breast or prostate cancer. A correlation of $\pm \geq 0.7$ represents a high correlation [27].

4. Results

4.1. Patient population

Between 2014 and 2019, a total of 500 patients were enrolled in 65 outpatient-centers specialized in medical oncology across Germany. Out of these, 496 patients were intended to be treated with antiresorptive treatment. Ten patients were excluded from analysis due to tumor location not being specified, wrong tumor entity or antiresorptive therapy was applied more than 7 days prior to study inclusion. The final analysis thus includes a data set of 486 patients with bone metastases, consisting of 176 patients (36%) with prostate cancer and 310 patients (64%) with breast cancer. A consort diagram is provided in Fig. 1.

Baseline demographic and clinical data are shown in Table 1. Median age at start of antiresorptive treatment was 76 years for prostate cancer patients vs. 67 years for breast cancer patients. 46.5% of breast cancer patients and 34.1% of prostate cancer patients had metastases not limited to bone. Patients were enrolled into the study at a median of 1.3 months after BM diagnosis.

About 95% of patients of both entities had not received any antiresorptive treatment before. 4.6% of prostate cancer patients and 4.9% of breast cancer patients had received prior antiresorptive therapy; as reason for prior antiresorptive therapy prophylaxis of osteoporosis was mostly reported (4.0% of prostate and 2.6% of breast cancer patients).

The median time between diagnosis of BM and start of antiresorptive therapy was 1.3 months for the total population, 1.6 months for prostate cancer patients and 1.2 months for breast cancer patients. 59.7% of patients with prostate and 79.7% of patients with breast cancer started antiresorptive therapy within 3 months after diagnosis of BM.

In total 59.5% of patients completed the observation period of 12 months (61.6% breast cancer, 56.8% prostate cancer). While 19% of breast cancer and 21% of prostate cancer patients died during the observation period, 18% of breast cancer and 22% of prostate cancer patients did not complete the observation period due to other reasons (lost-to-follow-up/ patient wish/ other).

4.2. Questionnaire return rate

In total, 3354 questionnaires were answered. At baseline 299 (97%) breast cancer and 175 (99%) prostate cancer patients answered the questionnaire. In months 3, 6, 9 and 12, 63.9%, 47.7%, 39.0%, 31.9% questionnaires of breast cancer patients and 59.7%, 48.4%, 44.3%, 24.4% questionnaires of prostate cancer patients were answered, respectively. After 6 months, questionnaires were available for almost 50% of included patients. Of the

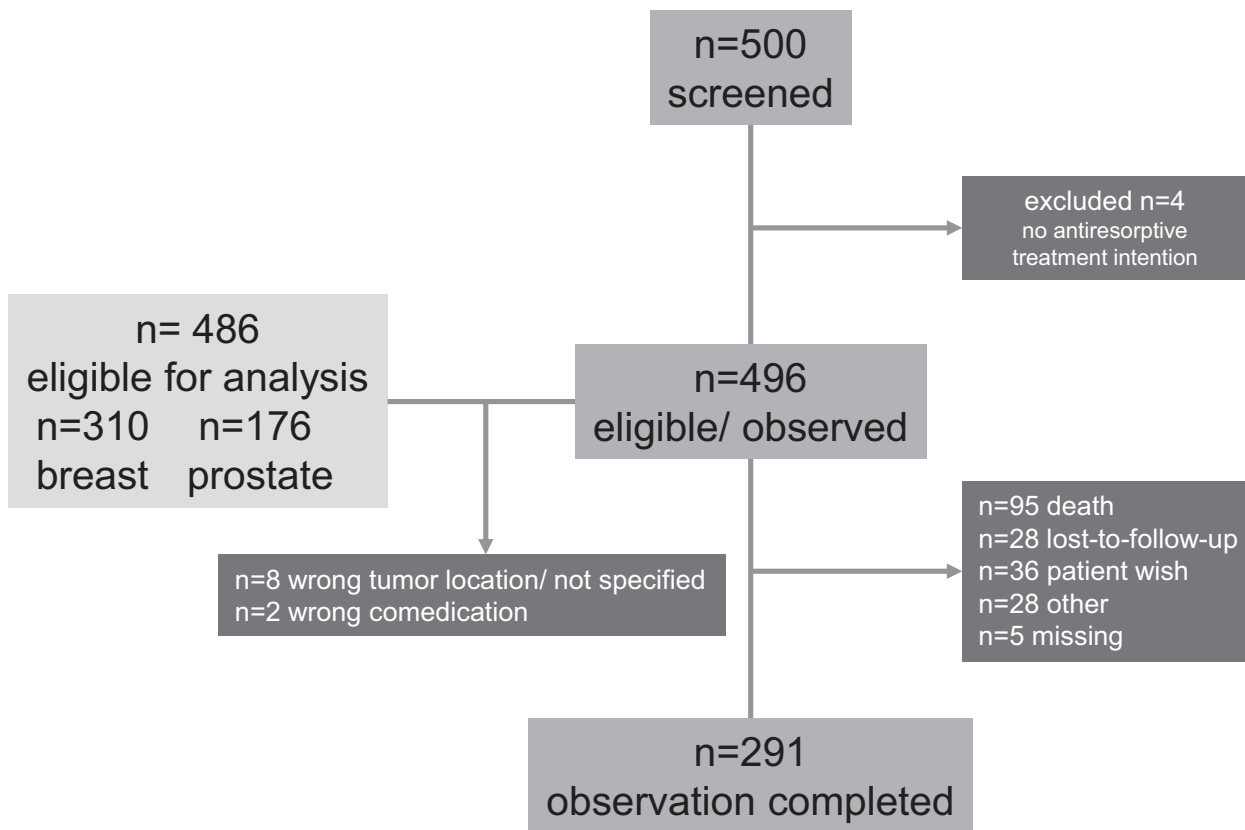


Fig. 1. Consort diagram. Patients were observed for a maximum of 12 months.

3354 questionnaires, 2962 (88.3%) had a maximum of one item missing. In total, 99.3% of questionnaires were evaluable for the FACT-BP-score and 98% of questionnaires were evaluable for the M-score. 97.9% and 98.7% of questionnaires were evaluable for general pain and bone pain, respectively.

4.3. Pain

At baseline, 77.2% of patients suffered from pain as assessed by the validated visual analog scale (VAS). About 15% of those patients rated pain intensity as ‘heavy’. Mean general pain levels of both,

breast and prostate cancer patients over time are depicted in Fig. 2A. In general, breast cancer patients reported a higher pain intensity compared to prostate cancer patients. For both breast and prostate cancer patients, reported pain levels decreased over time during the first three months of treatment. In the following months, pain slightly increased to a constant level, but lower than the initial pain level, for breast cancer patients. For prostate cancer patients, pain intensity levels went back to baseline values after three months. Looking at reported bone pain (assessed by item BP1 of the FACT-BP questionnaire), a very similar curve can be observed for mean bone pain levels (Fig. 2B). Mean FACT-

Table 1 Patient and tumor characteristics at baseline.

	Breast cancer n = 310	Prostate cancer n = 176
Age at inclusion		
Median in years (min, max)	67 (35, 92)	76.0 (52, 92)
Age categories (breast cancer / prostate cancer)		
<65 years / <75 years	130 (41.9%)	74 (42.0%)
≥65 years / ≥75 years	180 (58.1%)	102 (58.0%)
Sex		
Female	304 (98.1%)	
Male	6 (1.9%)	176 (100.0%)
Metastasis		
Bone only	166 (53.5%)	116 (65.9%)
Bone and other sites	144 (46.5%)	60 (34.1%)
Time from diagnosis of BM to study inclusion		
Median in months (min, max)	1.1 (0.0, 22.8)	1.6 (0.0, 24.9)
Time from diagnosis of BM to start of antiresorptive therapy		
Median in months (min, max)	1.2 (0.0, 22.6)	1.6 (0.0, 24.9)

BM bone metastases.

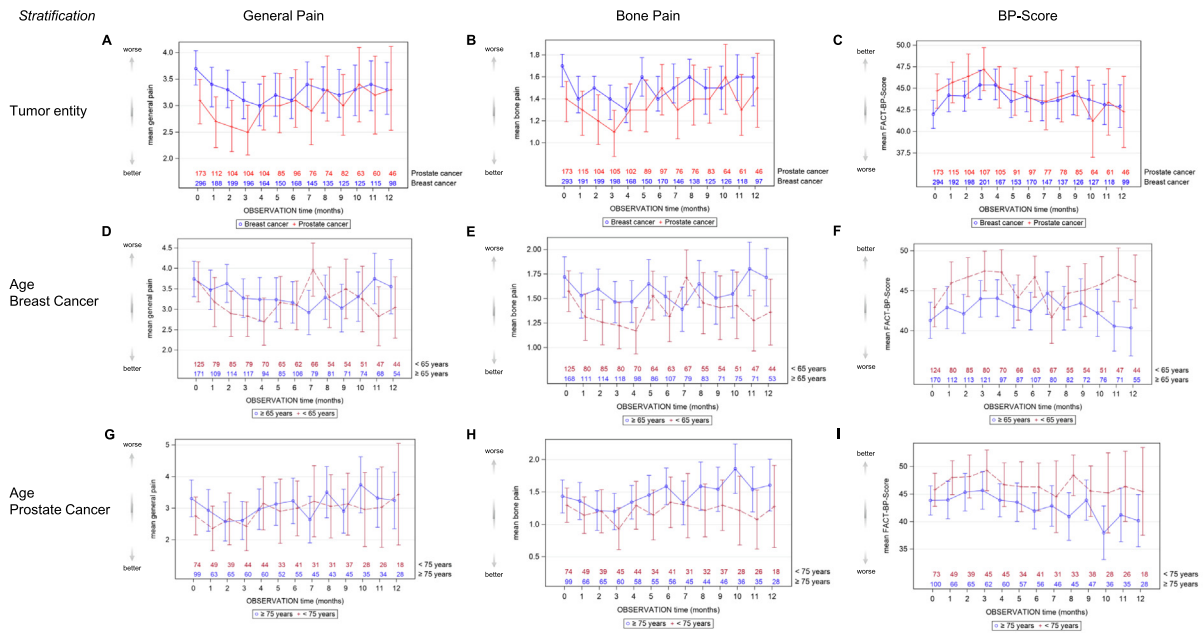


Fig. 2. Mean general pain (A, D, G), mean bone pain (B, E, H) and BP-Score/ QoL (C, F, I) stratified by tumor entity (A-C), age in breast cancer patients (D-F) and age in prostate cancer patients (G-I) over 12 months. Error bars represent the 95% confidence interval at each time point. For general pain and bone pain: higher values indicate more pain, for FACT-BP score: higher scores indicate a better QoL. QoL quality of life, FACT-BP Functional Assessment of Cancer Therapy – Bone Pain questionnaire. Only patients with evaluable questionnaires were considered for analysis. This might explain divergent patient numbers.

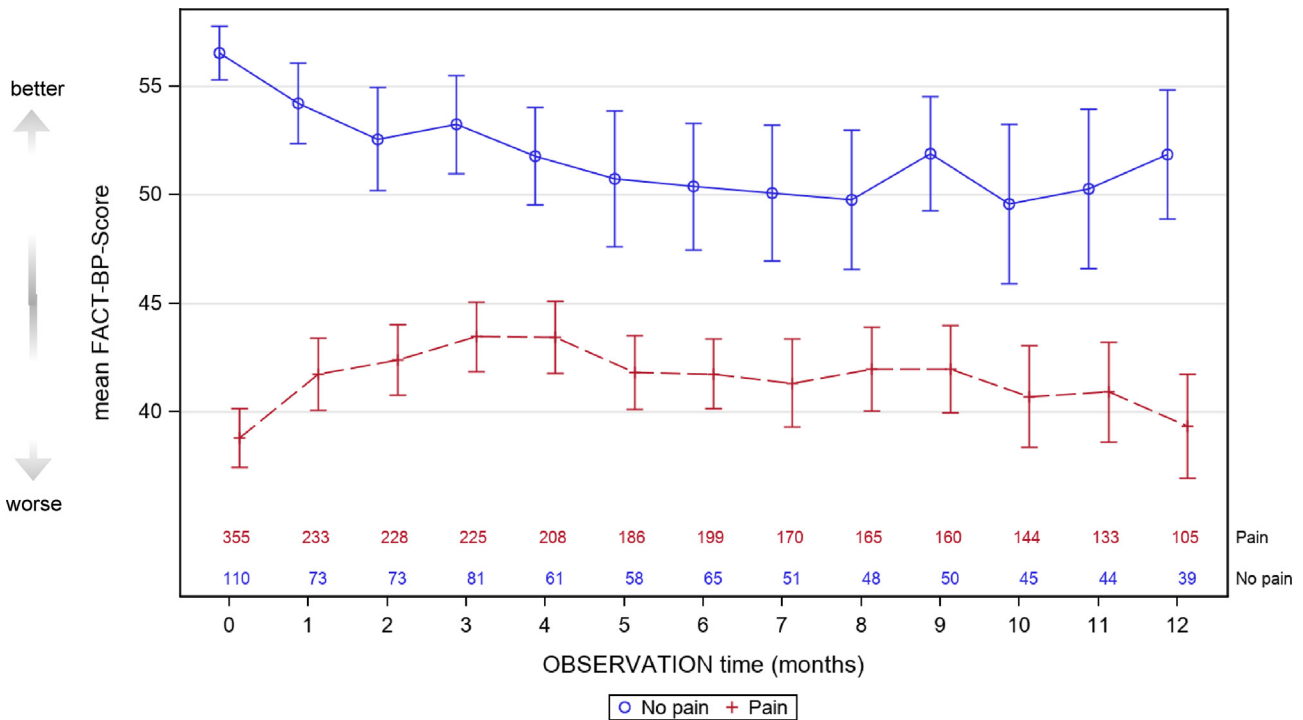


Fig. 3. Mean FACT-BP score/ QoL stratified by pain occurrence at baseline over 12 months. Error bars represent the 95% confidence interval at each time point. Higher scores indicate a better QoL. QoL quality of life, FACT BP Functional Assessment of Cancer Therapy Bone Pain. Only patients with evaluable questionnaires were considered for analysis. This might explain divergent patient numbers.

BP scores, reflecting patients QoL, for both entities are shown in Fig. 2C. The course was comparable with that of mean general pain and mean bone pain courses, with an improvement over the first months and a return to a constant level that is slightly above baseline level and about baseline level for breast and prostate cancer

patients, respectively. No differences were observed in mean general pain levels, mean bone pain levels and mean FACT-BP scores between the subgroups ‘age’ (<65 years vs. ‘≥65 years’, <75 years vs. ‘≥75 years’) (Fig. 2D-I), and ‘metastasis location’ (‘bone only’ vs. ‘bone and other sites’) (data not shown). About

50% of patients of both entities reported to use pain medication. This percentage remained constant during the whole observation period (breast cancer 48–60%; prostate cancer 42–52%). Effectiveness of pain medication was on average reported as ‘somewhat – quite a bit’. It equaled in both entities and age-groups and remained stable over the observation period (data not shown).

FACT-BP score categorized by general pain occurrence (‘no pain’ vs. ‘pain’) at baseline is shown in Fig. 3. For patients with no pain at baseline, FACT-BP scores slightly decreased during the first 3 months, while FACT-BP scores slightly increased during this time for patients who experienced pain at baseline, before reaching a plateau phase in both subgroups. However, throughout the whole observation period, patients without pain at baseline reported generally higher FACT-BP scores than patients with pain at baseline.

Upon categorization into three baseline bone pain-subgroups (‘no pain’, ‘tolerable pain’, ‘heavy pain’) there was also no overlapping of the mean FACT-BP score levels across the entire observation period (Fig. 4A). During course of treatment, FACT-BP scores deteriorate for patients starting with no bone pain, while FACT-BP scores of patients with tolerable pain remain at a constant level throughout observation and patients with heavy bone pain show improvement in FACT-BP scores over time. This effect was more prominent in older patients (breast cancer patients aged ‘ ≥ 65 years’ and prostate cancer patients ‘ ≥ 75 years’) than in younger subgroups (breast cancer patients aged ‘ < 65 years’ and prostate cancer patients ‘ < 75 years’) (data not shown).

Similar results were observed when categorizing into three baseline general pain-subgroups in the course of mean FACT-BP scores (Fig. 4B) as well as in the course of mean general pain levels (Fig. 4C).

4.4. Impact of time requirement for treatment of illness on daily life

The time course of reported M-scores (time-stress score) per age group and entity from baseline to twelve months is depicted in Fig. 5. Breast cancer patients in the subgroup ‘ < 65 years’ started and continued with comparable higher reported M-scores than older breast cancer patients (≥ 65 years) and prostate cancer patients. Looking at individual mean changes of M-scores from baseline, breast cancer patients show a decrease in M-scores, while M-scores of prostate patients were mainly unchanged over time. Furthermore, there were no differences in M-scores between subgroups ‘metastasis location’ (data not shown).

Correlation between BP-score and M-scores at baseline and at 12 months show a moderate negative relationship between both scores for prostate cancer patients at baseline (Pearson correlation coefficient -0.5) as well as at 12 months of treatment (-0.6). For breast cancer patients a respective negligible correlation of both scores was found (-0.39 at baseline and -0.29 at 12 months of treatment).

5. Discussion

Bone metastases cause severe pain, induce SREs like pathological fractures and spinal cord compression, and negatively affect daily functioning and QoL. The mechanisms leading to metastatic cancer-induced bone pain are complex and metastatic pain is multifactorial, involving chronic background pain as well as episodic breakthrough pain [28]. Therefore, different strategies need to be applied to achieve optimal pain relief and QoL. These include causal treatments like local surgery or radiotherapy, treatment with analgesics mainly for quick pain relief, and BTAs. BTAs are an important component of metastatic pain management because they not only reduce bone pain but also decrease the incidence of SREs and delay the time to SRE occurrence. The therapeutic goal

of metastatic pain management is pain relief but also the prevention of pain progression and SREs, and ultimately stabilization of patients QoL [29].

The aim of the PROBone real-world study was to evaluate bone metastasis related pain and health-related quality of life in patients with breast or prostate cancer under treatment with bone-targeting agents and to investigate correlations of baseline patient-characteristics using PRO. With the PROBone data, we could shed some more light onto some controversially discussed topics in the field.

Questionnaire return rate of PROBone resembles those of previous published work [30]. Considering that more than 40% of patients did not complete the observation period and thus, the number of patients who can possibly return questionnaires significantly drops over time, questionnaire return rates in PROBone can be rated as good. Close to 100% of questionnaires were evaluable.

It has been reported, that bone pain is a main factor accounting for QoL in patients with BM and can be used as a surrogate measure of QoL [20,21]. With our results, we could confirm this correlation by showing that curves for general pain, bone pain and FACT-BP scores show resembling characteristics. In the following “pain” is used as a surrogate for “general pain” and “bone pain”.

At study entry, more than 75% of patients already reported to suffer from pain and 15% of those reported pain intensity to be ‘heavy’. This is in line with data from other European real-world studies: In a study by von Moos et al., physicians reported that 79% of breast cancer patients were experiencing bone pain at time of BM diagnosis, compared to 73% of prostate cancer patients in a similar study by Body et al. [31,32]. Metastatic disease is often diagnosed due to pain as symptom. In a European survey conducted in 2010, bone metastases were identified during staging/diagnosis of primary cancer in 38% and as a result of bone pain in 35% of patients with solid cancer [33]. Interestingly, in that survey, in Germany bone pain resulted in BM diagnosis in only 20% of patients, while routine screening during follow-up was the main method of BM detection (41%). Regarding our current study, it is likely that a substantial proportion of the patients presenting with pain at start of BTA were diagnosed for BM due to pain only shortly before study entry.

However, there is also a substantial number of patients who present with asymptomatic metastasis and incidence and severity of bone pain are not necessarily proportionate to the number and size of bone metastases [28]. Approximately 25% of patients with bone metastases feel no pain [29]. This is in line with our data, where about 25% of patients with BM reported no pain at study start.

Nevertheless, current ESMO guidelines recommend initiating treatment with BTA as soon as metastasis is diagnosed in breast cancer and castration-resistant prostate cancer patients, whether the metastasis is symptomatic or not [19]. Of the patients included into the study, who all received BTA, 59.7% of patients with prostate and 79.7% of patients with breast cancer started antiresorptive therapy within 3 months after diagnosis of bone metastases. This number might be subject to a bias as patients treated shortly after diagnosis might be underrepresented in this study (mean time between diagnosis of BM and inclusion into the study was 1.3 months), which limits the interpretability of the data. On the other hand, numbers might be a bit too high due to a selection bias, as physicians who participated in the study probably are above-average aware of consequences of BM.

It is noticeable that especially in patients with prostate cancer, a considerable number (40.3%) of patients is treated relatively late during the disease (i.e. BTA treatment is started after 3 months of BM diagnosis or later). However, it should be noted that in prostate cancer, antiresorptive therapy is recommended dependent on the stage of the disease, i.e., it should only be given in the

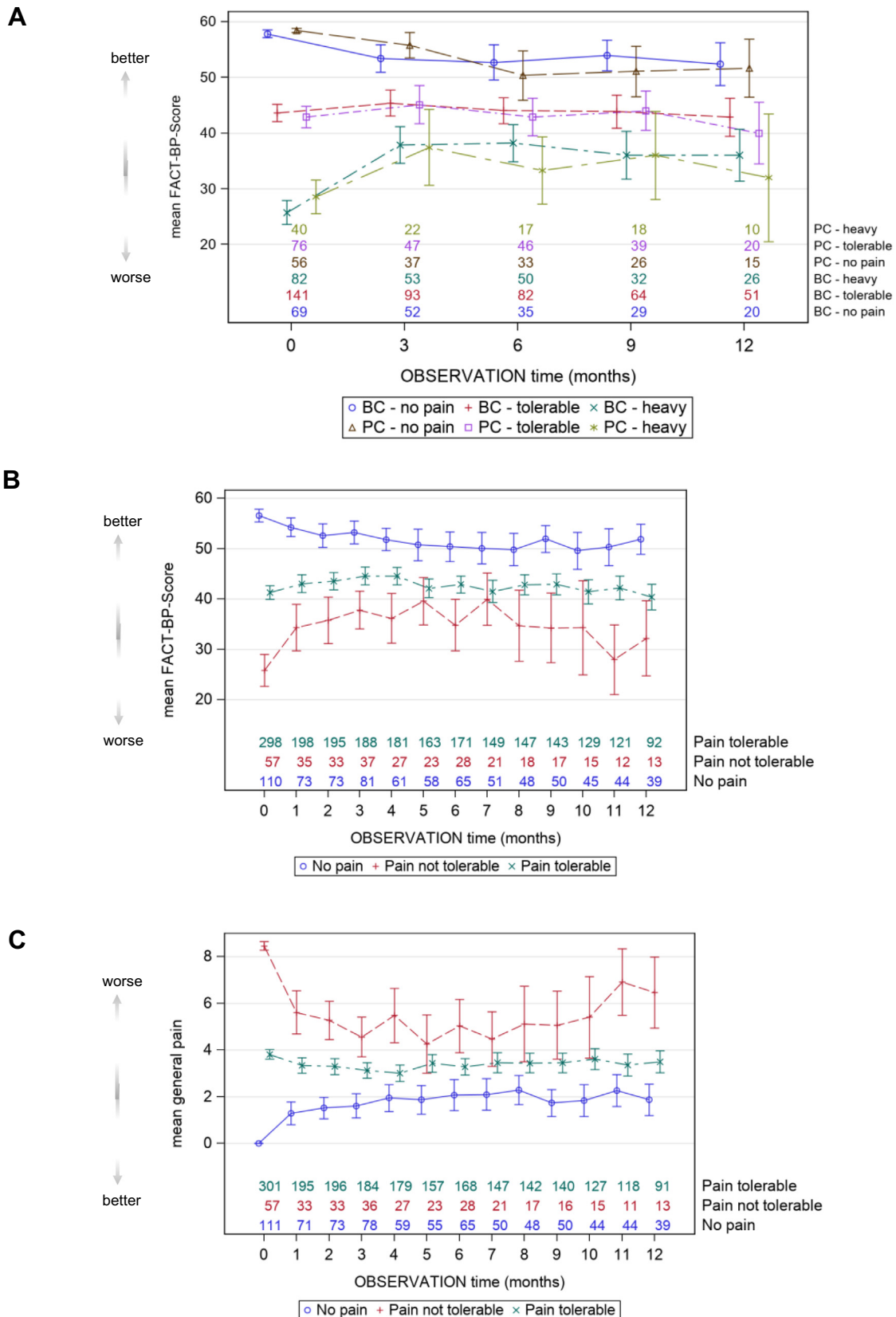


Fig. 4. Mean FACT-BP score/ QoL (A + B) and mean general pain (C) stratified by bone pain intensity (A) and general pain intensity (B + C) at baseline over 12 months. Error bars represent the 95% confidence interval at each time point. For general pain: higher values indicate more pain, for FACT-BP score: higher scores indicate a better QoL. BC breast cancer, FACT BP Functional Assessment of Cancer Therapy Bone Pain, PC prostate cancer, QoL quality of life. Only patients with evaluable questionnaires were considered for analysis. This might explain divergent patient numbers.

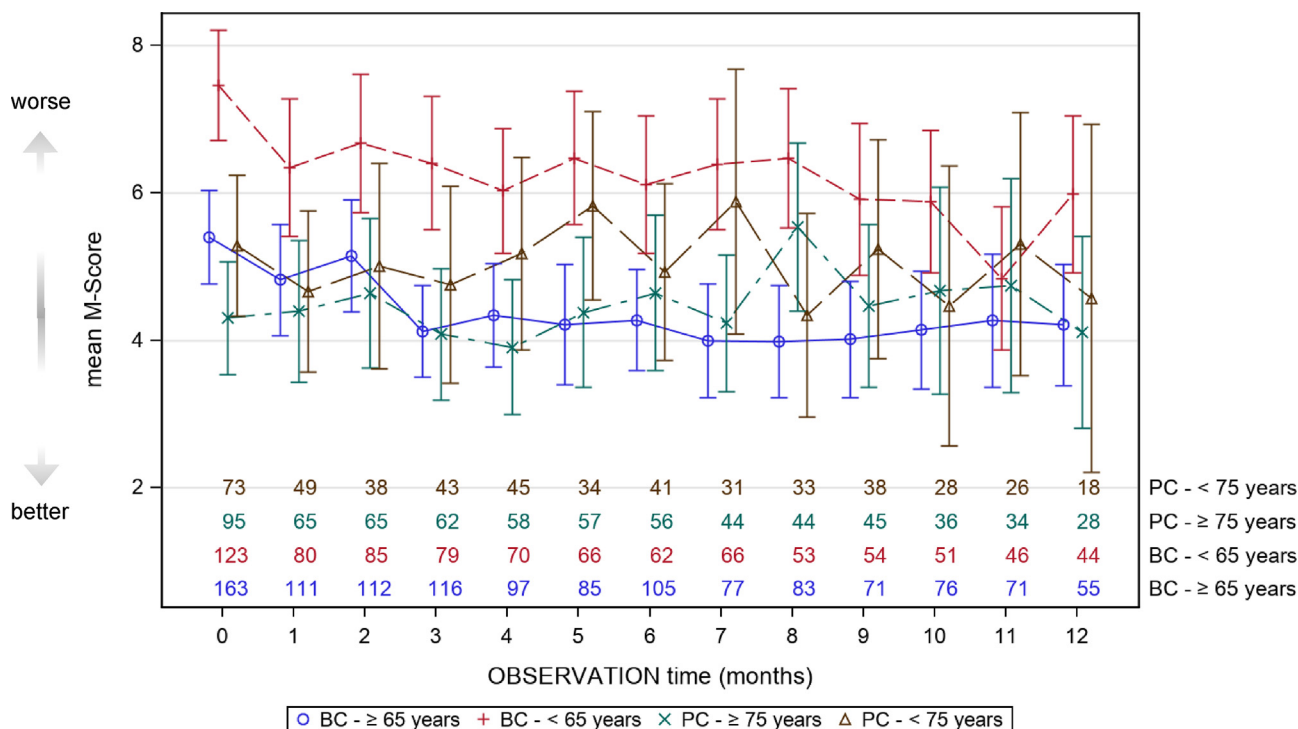


Fig. 5. Mean M-Score (time-stress score) stratified by age and entity. Error bars represent the 95% confidence interval at each time point. Higher values indicate a greater burden. Only patients with evaluable questionnaires were considered for analysis. This might explain divergent patient numbers.

castration-resistant setting and is not recommended for patients with hormone-sensitive prostate cancer [34,35].

Our data show that pain occurrence and intensity at onset of therapy with BTA is prognostic for further course of pain and QoL development. Thus, it appears increasingly important to start treatment as early as possible, ideally before pain onset. Patients without pain at baseline developed mild pain over the course of treatment, while patients starting with pain suffered from higher pain intensity levels over the whole observation period despite pain improvement and never reached pain levels as low as of patients that started without pain or tolerable pain. This is not only true for prognosis of pain development but also for QoL as reflected in FACT-BP-scores, with generally higher BP-scores and thus a better QoL over the whole observation period for patients starting without pain.

There are also examples in literature, where time from diagnosis of BM until start of therapy with BTA in breast cancer patients was shorter compared to PROBone as described for a clinical registry in Schröder et al. (22 days) [36]. It would be interesting to have pain and/or QoL data for this patient collective to evaluate progress of these parameters in a younger patient group (62.9 years median) treated closer to the time of diagnoses.

Although BTAs are generally well tolerated treatments, some rare but relevant side effects can occur that should be managed proactively, among them renal toxicity and osteonecrosis of the jaw. Osteonecrosis of the jaw is one of the most important side effects associated with BTA treatment. Therefore, ESMO practice guidelines as well as German evidence-based S3-guidelines for diagnosis and treatment of breast and prostate cancer strongly recommend oral examination and appropriate preventive dentistry before initiation of BTA therapy for all patients. During BTA therapy patients should receive regular dental/oral surgery review, avoid invasive dental procedures, and maintain good oral hygiene [19,37–39]. Regarding the German health care system, national guidelines provide additional in-depth recommendations on pro-

phylactic and preventive measures, as well as early interventions, helping to manage this relevant side effect [40].

We observed a clear pain reduction for the whole patient collective within the first treatment month, followed by further pain decrease over the consecutive 2–3 months, as well as an accompanying improvement in QoL. This effect of a quick first pain reduction by BTA is in line with the known pattern of action of BTA and is reported in literature [41]. The observed increase of pain in the following months to a plateau which remains below baseline for breast cancer patients is also in line with previous observations [42,43]. It can be speculated, why breast cancer patients initially report stronger pain and a poorer QoL compared to prostate cancer patients. Both gender and age could be reasons for the difference. Compared to older patients, younger patients might have a more active lifestyle, might still participate in working life and have more obligations. Pain could hinder maintenance of such a lifestyle and therefore be more wearing and sensed as more intense by younger patients compared to older patients, who might live a lifestyle allowing more rest and relaxation. Also, psychological burden that can differ between genders and age groups might affect sensation of pain.

It has been reported that analgesic management of bone pain is often insufficient and is performed in only up to 55% of patients with metastatic disease [44,45]. In our study, 42–60% of patients received analgesic pain medication during the observed treatment time. Considering that not all patients suffered from bone pain, administration of analgesic pain management in our study was satisfactory but there is still room for improvement. Education of physicians and patients along with enhanced communication might help to optimize pain therapy.

Looking at the impact of time requirements for treatment of cancer on daily life, which is assessed by the ‘M-score’ in our study, disturbance in daily life seems to be a bigger burden for younger patients, especially younger breast cancer patients. Similar to already discussed report of stronger pain, this could be

explained with a more active lifestyle of younger patients who are still in working life and experience more restrictions compared to older patients.

Our data represent prospectively collected real word data of an unselected patient collective that depicts treatment reality in Germany. However, our study also has limitations. The non-interventional design precludes causal conclusions on differences between subgroups. There might be a bias by physician selection as physicians with better awareness of issues related to bone metastasis might be more likely to participate in the study. Furthermore, it has to be considered that only about 60% of patients were documented until the end of the observation period. Moreover, our results should be interpreted within the limitations of the study design; data regarding association of pain or QoL with factors such as tumor burden, tumor control, use of BMA, use of analgesics or other interventions were not collected.

6. Conclusion

Early initiation of BTAs and adequate analgesia plays a key role in cancer pain management. Our results support current recommendations to initiate BTAs as soon as bone metastases are diagnosed to keep pain levels at the lowest level possible to minimize the debilitating effects of metastatic bone pain and to improve or maintain a good QoL as long as possible. Most patients received BTAs close to the time of diagnosis of BM, according to current recommendations, underscoring physicians' awareness of this important issue.

Funding

The study was financially supported by Amgen GmbH (Germany). AMGEN GmbH had no role in study design, data collection and analysis, interpretation of results, decision to publish, or preparation of the manuscript.

CRedit authorship contribution statement

Andreas Jakob: Conceptualization, Supervision, Resources, Writing – review & editing. **Mark-Oliver Zahn:** Supervision, Writing – review & editing. **Arnd Nusch:** Resources, Writing – review & editing. **Thorsten Werner:** Resources, Writing – review & editing. **Roland Schnell:** Resources, Writing – review & editing. **Melanie Frank:** Methodology, Software, Formal analysis, Data curation, Writing – review & editing. **Nicole Hamm:** Data curation, Writing – original draft, Writing – review & editing, Project administration. **Klaus-Ulrich Däßler:** . **Christoph Losem:** . **Manfred Welslau:** Resources, Writing – review & editing. **Petra Hoevel:** . **Karin Potthoff:** Writing – review & editing, Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors thank all patients, physicians and study nurses who participated in the PROBone study. We thank Dr. Judith Czarnecki (iOMEDICO) for writing and Dr. Christian Johansson (iOMEDICO) for critically reviewing the manuscript.

References

- [1] J.-J. Body, G. Quinn, S. Talbot, E. Booth, G. Demonty, A. Taylor, J. Amelio, Systematic review and meta-analysis on the proportion of patients with breast cancer who develop bone metastases, *Crit. Rev. Oncol./Hematol.* 115 (2017) 67–80, <https://doi.org/10.1016/j.critrevonc.2017.04.008>.
- [2] R.E. Coleman, Clinical Features of Metastatic Bone Disease and Risk of Skeletal Morbidity, *Clin. Cancer Res.* 12 (2006) 6243s–6249s, <https://doi.org/10.1158/1078-0432.CCR-06-0931>.
- [3] C. Parker, S. Nilsson, D. Heinrich, S.I. Helle, J.M. O'Sullivan, S.D. Fosså, A. Chodacki, P. Wiechno, J. Logue, M. Seke, A. Widmark, D.C. Johannessen, P. Hoskin, D. Bottomley, N.D. James, A. Solberg, I. Syndikus, J. Kliment, S. Wedel, S. Boehmer, M. Dall'Oglio, L. Franzén, R. Coleman, N.J. Vogelzang, C.G. O'Bryan-Tear, K. Staudacher, J. Garcia-Vargas, M. Shan, Ø.S. Bruland, O. Sartor, Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer (2013). <https://doi.org/10.1056/NEJMoa1213755>.
- [4] M.L. Svendsen, H. Gammelager, C. Sværke, M. Yong, V.M. Chia, C.F. Christiansen, J.P. Fryzek, Hospital visits among women with skeletal-related events secondary to breast cancer and bone metastases: a nationwide population-based cohort study in Denmark, *CLEP.* 5 (2013) 97–103, <https://doi.org/10.2147/CLEP.S42325>.
- [5] R. von Moos, J.J. Body, B. Egerdie, A. Stopeck, J. Brown, L. Fallowfield, D.L. Patrick, C. Cleeland, D. Damyanov, F.S. Palazzo, G. Marx, Y. Zhou, A. Braun, A. Balakumaran, Y. Qian, Pain and analgesic use associated with skeletal-related events in patients with advanced cancer and bone metastases, *Supportive Care in Cancer* : Official Journal of the Multinational Association of Support. Care Cancer 24 (2016) 1327–1337, <https://doi.org/10.1007/s00520-015-2908-1>.
- [6] D.L. Patrick, C.S. Cleeland, R. von Moos, L. Fallowfield, R. Wei, K. Öhrling, Y. Qian, Pain outcomes in patients with bone metastases from advanced cancer: assessment and management with bone-targeting agents, *Support. Care Cancer* 23 (2015) 1157–1168, <https://doi.org/10.1007/s00520-014-2525-4>.
- [7] R. von Moos, J.-J. Body, A. Rider, J. de Courcy, D. Bhowmik, F. Gatta, G. Hechmati, Y. Qian, Bone-targeted agent treatment patterns and the impact of bone metastases on patients with advanced breast cancer in real-world practice in six European countries, *Journal of Bone, Oncology.* 11 (2018) 1–9, <https://doi.org/10.1016/j.jbo.2017.11.004>.
- [8] J. Pereira, J.-J. Body, O. Gunther, H. Sleeboom, G. Hechmati, N. Maniadas, E. Terpos, Y.P. Acklin, J. Finek, R. von Moos, Cost of skeletal complications from bone metastases in six European countries, *J. Med. Econom.* 19 (2016) 611–618, <https://doi.org/10.3111/13696998.2016.1150852>.
- [9] A.T. Stopeck, A. Lipton, J.-J. Body, G.G. Steger, K. Tonkin, R.H. de Boer, M. Lichinitser, Y. Fujiwara, D.A. Yardley, M. Viniestra, M. Fan, Q. Jiang, R. Dansey, S. Jun, A. Braun, Denosumab Compared With Zoledronic Acid for the Treatment of Bone Metastases in Patients With Advanced Breast Cancer: A Randomized, Double-Blind Study, *JCO* 28 (2010) 5132–5139, <https://doi.org/10.1200/JCO.2010.29.7101>.
- [10] G. Selvaggi, G.V. Scagliotti, Management of bone metastases in cancer: A review, *Crit. Rev. Oncol./Hematol.* 56 (2005) 365–378, <https://doi.org/10.1016/j.critrevonc.2005.03.011>.
- [11] K. Fizazi, M. Carducci, M. Smith, R. Damião, J. Brown, L. Karsh, P. Milecki, N. Shore, M. Rader, H. Wang, Q. Jiang, S. Tadros, R. Dansey, C. Goessl, Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study, *The Lancet.* 377 (2011) 813–822, [https://doi.org/10.1016/S0140-6736\(10\)62344-6](https://doi.org/10.1016/S0140-6736(10)62344-6).
- [12] L.S. Rosen, D. Gordon, M. Kaminski, A. Howell, A. Belch, J. Mackey, J. Apffelstaedt, M. Hussein, R.E. Coleman, D.J. Reitsma, J.J. Seaman, B.L. Chen, Y. Ambros, Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial, *Cancer J.* 7 (2001) 377–387.
- [13] C. Van Poznak, M.R. Somerfield, W.E. Barlow, J.S. Biermann, L.D. Bosserman, M. J. Clemons, S.K. Dhesy-Thind, M.S. Dillmon, A. Eisen, E.S. Frank, R. Jagsi, R. Jimenez, R.L. Theriault, T.A. Vandenberg, G.C. Yee, B. Moy, Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology-Cancer Care Ontario Focused Guideline Update, *JCO.* 35 (2017) 3978–3986, <https://doi.org/10.1200/JCO.2017.75.4614>.
- [14] M.H. Wong, M.R. Stockler, N. Pavlakakis, Bisphosphonates and other bone agents for breast cancer, *Cochr. Datab. Systemat. Rev.* (2012), <https://doi.org/10.1002/14651858.CD003474.pub3>.
- [15] A. Lipton, K. Fizazi, A.T. Stopeck, D.H. Henry, J.E. Brown, D.A. Yardley, G.E. Richardson, S. Siena, P. Maroto, M. Clemens, B. Bilynsky, V. Charu, P. Beuzeboc, M. Rader, M. Viniestra, F. Saad, C. Ke, A. Braun, S. Jun, Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: A combined analysis of 3 pivotal, randomised, phase 3 trials, *Eur. J. Cancer* 48 (2012) 3082–3092, <https://doi.org/10.1016/j.ejca.2012.08.002>.
- [16] E. Gonzalez-Rodriguez, B. Aubry-Rozier, D. Stoll, K. Zaman, O. Lamy, Commentary to “Denosumab for bone health in prostate and breast cancer patients receiving endocrine therapy? A systematic review and a meta-analysis of randomized trials” (Galvano *J Bone Oncol*, et al. 18:100252), *J. Bone Oncol.* 22 (2020) (2019), <https://doi.org/10.1016/j.jbo.2020.100294>.
- [17] A. Galvano, D. Scaturro, G. Badalamenti, L. Incorvaia, S. Rizzo, L. Castellana, S. Cusenza, S. Cutaia, D. Santini, F. Guadagni, M. Roselli, S. Gori, M.A. Latteri, V. Bazan, L.M. Giulia, A. Russo, Denosumab for bone health in prostate and breast cancer patients receiving endocrine therapy? A systematic review and a meta-

- analysis of randomized trials, *J. Bone Oncol.* 18 (2019), <https://doi.org/10.1016/j.jbo.2019.100252> 100252.
- [18] M. AlZahrani, M. Clemons, L. Vandermeer, M. Sienkiewicz, A.A. Awan, B. Hutton, G.R. Pond, T.L. Ng, Real-world practice patterns and attitudes towards de-escalation of bone-modifying agents in patients with bone metastases from breast and prostate cancer: A physician survey, *J. Bone Oncol.* 26 (2021), <https://doi.org/10.1016/j.jbo.2020.100339> 100339.
- [19] R. Coleman, P. Hadji, J.-J. Body, D. Santini, E. Chow, E. Terpos, S. Oudard, Ø. Bruland, P. Flamen, A. Kurth, C.V. Poznak, M. Aapro, K. Jordan, Bone health in cancer: ESMO Clinical Practice Guidelines, *Ann. Oncol.* 31 (2020) 1650–1663, <https://doi.org/10.1016/j.annonc.2020.07.019>.
- [20] I.J. Diel, Effectiveness of bisphosphonates on bone pain and quality of life in breast cancer patients with metastatic bone disease: a review, *Support. Care Cancer* 15 (2007) 1243, <https://doi.org/10.1007/s00520-007-0244-9>.
- [21] L. Costa, P.P. Major, Effect of bisphosphonates on pain and quality of life in patients with bone metastases, *Nat. Rev. Clin. Oncol.* 6 (2009) 163–174, <https://doi.org/10.1038/nrponc1323>.
- [22] D.-T. Wen, Z. Xu, M.-L. Xuan, G.-R. Liang, W.-L. Zheng, X.-F. Liang, J. Xiao, X.-Y. Wang, Prognostic Effect of Bisphosphonate Exposure for Patients With Diagnosed Solid Cancer: A Systematic Review With Meta-Analysis of Observational Studies accessed February 3, 2022 *Front. Oncol.* 8 (2018), <https://www.frontiersin.org/article/10.3389/fonc.2018.00495>.
- [23] F. Saad, D.M. Gleason, R. Murray, S. Tchekmedyian, P. Venner, L. Lacombe, J.L. Chin, J.J. Vinholes, J.A. Goas, M. Zheng, For the Zoledronic Acid Prostate Cancer Study Group, Long-Term Efficacy of Zoledronic Acid for the Prevention of Skeletal Complications in Patients With Metastatic Hormone-Refractory Prostate Cancer, *JNCI: J. Natl. Cancer Institute.* 96 (2004) 879–882, <https://doi.org/10.1093/jnci/djh141>.
- [24] R. Broom, H. Du, M. Clemons, D. Eton, G. Dranitsaris, C. Simmons, W. Ooi, D. Cella, Switching Breast Cancer Patients with Progressive Bone Metastases to Third-Generation Bisphosphonates: Measuring Impact Using the Functional Assessment of Cancer Therapy-Bone Pain, *J. Pain Symptom Manage.* 38 (2009) 244–257, <https://doi.org/10.1016/j.jpainsymman.2008.08.005>.
- [25] D.A. Delgado, B.S. Lambert, N. Boutris, P.C. McCulloch, A.B. Robbins, M.R. Moreno, J.D. Harris, Validation of Digital Visual Analog Scale Pain Scoring With a Traditional Paper-based Visual Analog Scale in Adults, *JAAOS Global Res. Rev.* 2 (2018), <https://doi.org/10.5435/JAAOSGlobal-D-17-00088> e088.
- [26] FACT-BP, FACIT Group. (n.d.). <https://www.facit.org/measures/FACT-BP> (accessed February 2, 2022).
- [27] M.M. Mukaka, Statistics corner: A guide to appropriate use of correlation coefficient in medical research, *Malawi Med J.* 24 (2012) 69–71.
- [28] T. Middlemiss, B.J.A. Laird, M.T. Fallon, Mechanisms of Cancer-induced Bone Pain, *Clin. Oncol.* 23 (2011) 387–392, <https://doi.org/10.1016/j.clon.2011.03.003>.
- [29] R. Zajackowska, M. Kocot-Kępska, W. Leppert, J. Wordliczek, Bone Pain in Cancer Patients: Mechanisms and Current Treatment, *Int. J. Mol. Sci.* 20 (2019) 6047, <https://doi.org/10.3390/ijms20236047>.
- [30] I. Kuchuk, J.L. Beaumont, M. Clemons, E. Amir, C.L. Addison, D. Cella, Effects of de-escalated bisphosphonate therapy on the Functional Assessment of Cancer Therapy-Bone Pain, Brief Pain Inventory and bone biomarkers, *J. Bone Oncol.* 2 (2013) 154–157, <https://doi.org/10.1016/j.jbo.2013.07.004>.
- [31] J.-J. Body, R. von Moos, A. Rider, P. Hallworth, D. Bhowmik, F. Gatta, G. Hechmati, Y. Qian, A real-world study assessing the use of bone-targeted agents and their impact on bone metastases in patients with prostate cancer treated in clinical practice in Europe, *J. Bone Oncol.* 14 (2019), <https://doi.org/10.1016/j.jbo.2018.100212> 100212.
- [32] R. von Moos, J.-J. Body, A. Rider, J. de Courcy, D. Bhowmik, F. Gatta, G. Hechmati, Y. Qian, Bone-targeted agent treatment patterns and the impact of bone metastases on patients with advanced breast cancer in real-world practice in six European countries, *J. Bone Oncol.* 11 (2018) 1–9, <https://doi.org/10.1016/j.jbo.2017.11.004>.
- [33] T. Lebret, A. Casas, M. Cavo, P.J. Woll, C. Deleplace, C. Kennedy, P. Schoen, C. Jackisch, The use of bisphosphonates in the management of bone involvement from solid tumours and haematological malignancies – a European survey, *Europ. J. Cancer.* 26 (2017), <https://doi.org/10.1111/ecc.12490> e12490.
- [34] A. Lipton, R.L. Theriault, G.N. Hortobagyi, J. Simeone, R.D. Knight, K. Mellars, D. J. Reitsma, M. Heffernan, J.J. Seaman, Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases, *Cancer* 88 (2000) 1082–1090, [https://doi.org/10.1002/\(SICI\)1097-0142\(20000301\)88:5<1082::AID-CNCR20>3.0.CO;2-Z](https://doi.org/10.1002/(SICI)1097-0142(20000301)88:5<1082::AID-CNCR20>3.0.CO;2-Z).
- [35] M. Trinkaus, C. Simmons, J. Myers, G. Dranitsaris, M. Clemons, Skeletal-related events (SREs) in breast cancer patients with bone metastases treated in the nontrial setting, *Support. Care Cancer* 18 (2009) 197, <https://doi.org/10.1007/s00520-009-0645-z>.
- [36] J. Schröder, T. Fietz, A. Köhler, V. Petersen, H. Tesch, L. Spring, A. Fleitz, M. Jänicke, N. Marschner, Treatment and pattern of bone metastases in 1094 patients with advanced breast cancer – Results from the prospective German Tumour Registry Breast Cancer cohort study, *Eur. J. Cancer* 79 (2017) 139–148, <https://doi.org/10.1016/j.ejca.2017.03.031>.
- [37] N. Yarom, C.L. Shapiro, D.E. Peterson, C.H. Van Poznak, K. Bohlke, S.L. Ruggiero, C.A. Migliorati, A. Khan, A. Morrison, H. Anderson, B.A. Murphy, D. Alston-Johnson, R.A. Mendes, B.M. Beadle, S.B. Jensen, D.P. Saunders, Medication-Related Osteonecrosis of the Jaw: MASCC/ISOO/ASCO Clinical Practice Guideline, *JCO.* 37 (2019) 2270–2290, <https://doi.org/10.1200/JCO.19.01186>.
- [38] Guidelines Program Oncology (German Cancer Society, German Cancer Aid, AWMF):S3-Leitlinie Früherkennung, Diagnose, Therapie und Nachsorge desMammakarzinoms, Version 4.4, 2021,AWMF Registernummer:032-0450L, <http://www.leitlinienprogramm-onkologie.de/leitlinien/mammakarzinom/> (retrieved on: 03.02.2022), (2021) 467.
- [39] Guidelines Program Oncology (German Cancer Society, German Cancer Aid, AWMF): S3-Leitlinie Prostatakarzinom, Langversion 6.2, 2021,AWMF Registernummer: 043/0220L, <http://www.leitlinienprogramm-onkologie.de/leitlinien/prostatakarzinom/> (retrieved on: 03.02.2022), (n.d.). <https://www.leitlinienprogramm-onkologie.de/leitlinien/prostatakarzinom/> (accessed February 3, 2022).
- [40] O. Ristow, P. Voss, K.A. Grötz, S3-Leitlinie Antiresorptiva-assoziierte Kiefernekrosen [2017], AWMF Registernummer: 007-091, Schiegnitz E, Al-Nawas B, Hoefert S, Otto S, Pautke C, Ristow O, Voss P, Grötz KA, (2018) 67.
- [41] J. Gralow, D. Tripathy, Managing Metastatic Bone Pain: The Role of Bisphosphonates, *J. Pain Symptom Manage.* 33 (2007) 462–472, <https://doi.org/10.1016/j.jpainsymman.2007.01.001>.
- [42] J.-J. Body, I.J. Diel, M.R. Lichinitser, E.D. Kreuser, W. Dornoff, V.A. Gorbunova, M. Budde, B. Bergström, Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases, *Ann. Oncol.* 14 (2003) 1399–1405, <https://doi.org/10.1093/annonc/mdg367>.
- [43] I.J. Diel, J.-J. Body, M.R. Lichinitser, E.D. Kreuser, W. Dornoff, V.A. Gorbunova, M. Budde, B. Bergström, Improved quality of life after long-term treatment with the bisphosphonate ibandronate in patients with metastatic bone disease due to breast cancer, *Eur. J. Cancer* 40 (2004) 1704–1712, <https://doi.org/10.1016/j.ejca.2004.03.025>.
- [44] S. Deandrea, M. Montanari, L. Moja, G. Apolone, Prevalence of undertreatment in cancer pain. A review of published literature, *Ann. Oncol.* 19 (2008) 1985–1991, <https://doi.org/10.1093/annonc/mdn419>.
- [45] G. Apolone, O. Corli, A. Caraceni, E. Negri, S. Deandrea, M. Montanari, M.T. Greco, Pattern and quality of care of cancer pain management. Results from the Cancer Pain Outcome Research Study Group, *Br. J. Cancer.* 100 (2009) 1566–1574, <https://doi.org/10.1038/sj.bjc.6605053>.