



## Research Paper

# 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

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## ABSTRACT

**Background:** Bone metastases (BMs) are common in patients with breast cancer and can lead to skeletal-related events (SREs), which are associated with increased pain and reduced quality of life (QoL). Bone-targeted agents (BTAs), like zoledronic acid and denosumab, reduce the incidence of SREs and delay progression of bone pain. **Materials and methods:** We evaluated the management of BMs and pain in six European countries (Belgium, France, Germany, Italy, Spain, and UK) using the Adelphi Breast Cancer Disease Specific Programme, which included a physician survey and patient-reported outcomes (PROs) to assess the impact of BMs on pain and QoL. **Results:** 301 physicians completed patient record forms for 2984 patients with advanced breast cancer; 1408 with BMs and 1136 with metastases at sites other than bone (non-BMs). Most patients with BMs (88%) received a BTA, with 81% receiving treatment during 3 months following BM diagnosis. For those who did not receive a BTA, the main reasons given were: very recent BM diagnosis, perceived low risk of bone complications, and short life expectancy. Most patients with BMs (68%) were experiencing bone pain and, of these, 97% were taking analgesics (including 28% receiving strong opioids). Despite this, moderate to severe pain was reported in 20% of patients who were experiencing pain. PROs were assessed in 766 patients with advanced breast cancer (392 with BMs, 374 with non-BMs). Overall, patients with BMs reported worse pain and QoL outcomes than those with non-BMs, those not receiving a BTA reported worse pain.

**Conclusion:** Despite the large proportion of patients receiving BTAs in this study, some patients with BMs are still not receiving early treatment to prevent SREs or to manage pain. Improving physicians' understanding of the role of BTAs and the importance of early treatment following BM diagnosis has the potential to improve patient care.

## 1. Introduction

Bone is the most common site affected by metastatic cancer: a recent meta-analysis reported that bone metastases (BMs) occur in 58% of patients with advanced breast cancer [1]. BMs often cause debilitating bone pain and lead to bone complications, known as skeletal-related events (SREs; commonly defined as radiation or surgery to bone,

pathologic fracture, spinal cord compression, or hypercalcemia of malignancy) [2]. SREs cause pain, impair physical activity, negatively affect quality of life (QoL), and are associated with increased mortality [3–5]. Clinical trial data show that, if patients do not receive treatment to prevent SREs, 64% of women with breast cancer and BMs develop an SRE [6]. In the real-world setting, the SRE incidence is probably lower than that from clinical trials. This may be because symptomatic SREs

**Abbreviations:** BMs, bone metastases; BPI, Brief Pain Inventory; BTA, bone-targeted agent; CI, confidence interval; DSP, Disease Specific Programme; EQ-5D, 5-dimension (3-level) EuroQol questionnaire; ER, estrogen receptor; FACT-B, Functional Assessment of Cancer Therapy – Breast questionnaire; HER2, human epidermal growth factor receptor 2; ONJ, osteonecrosis of the jaw; PRO, patient-reported outcome; PRF, Patient Record Form; PSCF, Patient Self-Completion Form; QoL, quality of life; SRE, Skeletal-related event; ZA, zoledronic acid

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(SSEs) are more likely to be collected than SREs and reflects real-world practice that some patients may receive treatment to prevent SREs. The high prevalence of SREs in patients with advanced breast cancer reflects both the high incidence of BMs [7] and the relatively long survival times in these patients [8]; metastatic breast cancer at diagnosis is associated with 3-year and 5-year survival rates of approximately 35% [9] and 26%, respectively [10]. Patients with BMs generally survive for longer than patients with other metastatic sites (such as liver, brain, or lung) [11]. Furthermore, individuals with advanced breast cancer may experience several SREs during the course of their disease [12], and having one SRE increases a patient's risk of experiencing subsequent SREs [13]. These bone complications therefore place a considerable burden on both patients and healthcare resources [14–16].

Bone-targeted agents (BTAs), such as the bisphosphonate zoledronic acid (ZA) and denosumab, reduce the incidence of SREs [17,18] and delay the progression of bone pain [19]. ZA is administered as a 4 mg intravenous infusion every 3–4 weeks [17]; denosumab, a fully human immunoglobulin G2 monoclonal antibody against the receptor activator of nuclear factor kappa B ligand, is administered as a 120 mg subcutaneous injection every 4 weeks [18]. These therapies have both been shown to delay SREs [17,18] and reduce pain levels in patients with moderate to severe pain [19]; denosumab has been shown to be more effective than ZA at delaying and preventing SREs, preventing the worsening of pain associated with BMs, and delaying the need for strong opioids [19]. Both agents are recommended for patients with BMs whether they are symptomatic or not [20]. Pain is often under-reported and poorly managed in patients with cancer [21]. In a phase 3 trial evaluating denosumab versus ZA in patients with BMs secondary to breast cancer, 43% of patients had moderate to severe bone pain at the start of BTA treatment; however, fewer than 20% of these patients were receiving strong opioids [22]. Little is known about the utilization pattern of BTAs and the impact of BMs in real-world practice.

## 2. Aims

This study aimed to describe the treatment pattern of BTAs in patients with breast cancer and BMs, including the reasons guiding treatment decisions, in a real-world setting in Europe. Furthermore, by using validated instruments to collect patient-reported outcomes (PROs), we aimed to understand the impact of BMs on patients' experiences of pain and QoL.

## 3. Methods

### 3.1. Physicians and patients

Data were collected using the Adelphi Breast Cancer Disease Specific Programme (DSP), an independent multi-country, cross-sectional survey of physicians. The full DSP methodology has been described previously [23]. The study was conducted between February and April 2015 in six European countries comprising Belgium, France, Germany, Italy, Spain, and the UK. Physicians were selected from publicly available lists of healthcare professionals, and were approached to take part in the study by field-based interviewers. The study aimed to gain participation from 300 physicians (60 in each of France, Germany, Italy, and Spain, 50 in the UK, and 10 in Belgium). To be eligible for inclusion in the study, physicians had to have: medically qualified as an oncologist between 1978 and 2011; been seeing a minimum of five patients with breast cancer per week; and been personally responsible for prescribing decisions for patients with advanced breast cancer.

Participating physicians reported data for the next eight consecutive adult (aged  $\geq 18$  years) female patients they saw in their clinic who had been diagnosed with advanced breast cancer (stage IIIB–IV) and who were not currently enrolled in a clinical trial. Physicians also collected data from a further two patients with the additional criterion of a BM

diagnosis. Physicians captured data using a detailed Patient Record Form (PRF) for each of the 10 patients; data were included regardless of how many patients physicians filled out a PRF. All patients for whom a physician completed a PRF were invited to complete a voluntary Patient Self-Completion Form (PSCF). Informed consent was obtained from patients before they completed this form.

### 3.2. Study variables

Data on patient baseline characteristics were extracted from all the PRFs. For patients with a BM diagnosis the following data were also collected from the PRFs: presence of bone pain (at initial diagnosis of BMs and at time of data collection – pain was classified as mild, moderate, or severe according to the Brief Pain Inventory [BPI]) [24]; analgesic use (measured using the modified Analgesic Quantification Algorithm [25], which scores analgesic use from 0 for no analgesic to 7 for strong opioid [ $> 600$  mg/day oral morphine equivalent]); time from initial breast cancer diagnosis to BM diagnosis; time from BM diagnosis to the date of data collection; whether a BTA was prescribed; time from BM diagnosis to BTA treatment initiation; which BTA was prescribed; the dose of BTA; discontinuation of a BTA; and switching from one BTA to another.

Physicians were asked to rank up to three reasons from a predefined list for: treating or not treating patients with a BTA; choosing one BTA over another; changing BTA dose; switching from one BTA agent to another; and discontinuing BTA therapy. To understand whether BTA treatment was initiated immediately after BM diagnosis or not, a cutoff period of 3 months from diagnosis of BMs to treatment initiation was used. Physicians were asked to rank their reasons for initiating BTA treatment early ( $\leq 3$  months of BM diagnosis) or for delaying BTA treatment ( $> 3$  months after BM diagnosis).

The PSCFs incorporated three instruments to facilitate the collection of PRO data on pain and QoL from patients with BMs and from those with metastases located at sites other than the bone (non-BMs) which included the BPI [24], the 5-dimension 3-level EuroQol questionnaire (EQ-5D), the EuroQol visual analog scale (EQ-VAS) [26], the Functional Assessment of Cancer Therapy – Breast questionnaire (FACT-B), and the Functional Assessment of Cancer Therapy – General questionnaires [27].

### 3.3. Statistical analyses

Patient characteristics and outcome variables were analyzed using descriptive statistics. Frequencies (%) were calculated for categorical or ordinal variables, and means and medians (interquartile ranges) for continuous variables. PROs for patients with BMs and those with non-BMs were compared using the univariate Mann–Whitney test and multivariable linear regression analysis (adjusting for confounding factors: age, smoking status, time since diagnosis of breast cancer, positive estrogen receptor [ER] status, positive human epidermal growth factor receptor 2 [HER2] status, and number of additional comorbidities).

## 4. Results

### 4.1. Physician characteristics

In total, 301 oncologists (11 in Belgium, 55 in France, 62 in Germany, 61 in Italy, 61 in Spain, and 51 in the UK) provided data via PRFs. Of these, 84 physicians stated that they worked in an office setting; 73% worked in public practice and 26% in private practice.

### 4.2. Patient characteristics

Data were collected for 2984 patients with advanced breast cancer. Of these, 2544 had metastatic (stage IV) cancer, including 1408 with

**Table 1**  
Patient demographics and clinical characteristics.

	Patients with BMs (n = 1408)	Patients with non-BMs (n = 1136)	Patients with stage IIIb/c breast cancer (n = 440)
Age, mean (SD) for those aged < 90 years	64.7 (11.6)	62.9 (11.5)	58.5 (11.8)
Postmenopausal, n (%)	1213 (86)	946 (83)	311 (71)
Family history of breast or ovarian cancer, n (%)	135 (10)	110 (10)	66 (15)
Time since breast cancer diagnosis, months, median (25–75th percentiles)	11.9 (3.0–36.2)	12.4 (3.4–29.5)	6.7 (2.6–23.0)
HR status, n (%)			
HR positive	1080 (77)	732 (64)	248 (56)
HR negative	300 (21)	393 (35)	108 (25)
Unknown	28 (2)	11 (1)	84 (19)
Most common anti-cancer treatments, n (%)			
Letrozole	278 (20)	78 (7)	25 (6)
Paclitaxel and bevacizumab	94 (7)	97 (9)	7 (2)
Capecitabine	79 (6)	97 (9)	14 (3)
Paclitaxel	78 (6)	80 (7)	25 (6)
Docetaxel	38 (3)	69 (6)	38 (9)
Anastrozole	80 (6)	41 (4)	14 (3)
Other, medication < 5% of patients each	761 (54)	674 (59)	317 (72)

Data shown are n (%) unless otherwise stated. BMs, bone metastases; HR, hormone receptor; non-BMs, metastases at sites other than bone; SD, standard deviation.

BM and 1136 with non-BMs. Baseline characteristics for all patients are presented in Table 1. Of the patients with BMs, 53% (n = 752) had bone-only metastases. Of those individuals with BMs, 100 from Belgium, 312 were from France, 239 from Germany, 202 from Italy, 299 from Spain, and 256 from the UK. The baseline characteristics of these patients were broadly similar across the six European countries with the exception of median time since breast cancer diagnosis, which was shorter in Belgium (3.0 months) than in the other countries studied (7.8–13.4 months) (Supplementary Table 1).

Of the 1408 patients with BMs, 1043 were considered to be at either a low risk (n = 251) or a high risk (n = 792) of bone complications at the time the initial BTA treatment decision was made, based on their physician's clinical opinion. For individuals at high risk of bone complications the most common sites of BMs were the vertebrae (80% at high risk vs. 65% at low risk), hip or pelvic bone (52% vs. 47%, respectively), and ribs (36% vs. 42%, respectively). BMs occurred in the long bones (leg, arm, or rib) in 46% of patients at high risk and in 51% of those at low risk of bone complications. Compared with patients at low risk of bone complications, those at high risk were significantly more likely to have BMs in the vertebrae (p < 0.001). Patients at a perceived high risk of bone complications had BMs at significantly more skeletal locations than those considered to be at low risk (mean [standard deviation], 2 [1] vs. 1.8 [0.9], respectively; p = 0.006).

4.3. Bone-targeted agent treatment patterns

Among patients with BMs, 88% (n = 1238) were receiving a BTA (Fig. 1) and 81% of these (n = 1003) had initiated treatment during the 3 months following BM diagnosis (early initiation). The main reasons given by physicians for initiating BTA treatment early were that the

patient was experiencing bone pain (33% of patients; n = 336) and that the patient was considered to be at high risk of developing bone complications (31%; n = 313). These results for the overall European cohort were broadly reflected across individual countries (Table 2). The main reason given by physicians for delaying BTA treatment (> 3 months from BM diagnosis) (19% of BTA-treated patients; n = 235) was because of very recent BM diagnosis (23%; n = 55); however, results varied slightly across countries (Table 3). Of the 170 patients with BMs who were not receiving a BTA, the top three reasons given by physicians for not initiating BTA treatment were: very recent diagnosis (41%; n = 70); a low perceived risk of bone complications (18%; n = 30); and short life expectancy (10%; n = 17). The cost impact on the patient, hospital, or healthcare system in their decision whether to treat with a BTA was cited by five (2%) physicians.

Of those treated with BTAs, the majority of patients received either ZA (48%; n = 591) or denosumab (47%; n = 579) as a first BTA (Fig. 1). The main reasons physicians specified for choosing ZA were: clinical efficacy in delaying onset of SREs (34%; n = 199); long-term safety (14%; n = 83); and reducing the risk of SREs (14%; n = 82). The main reasons for choosing denosumab were: clinical efficacy in delaying the onset of SREs (37%; n = 217); reducing the risk of SREs (15%; n = 89); mode of administration (13%; n = 74); and efficacy in reducing the number of SREs (10%; n = 57). Most patients prescribed ZA received it every 3 or 4 weeks (97%; n = 573) and most individuals receiving denosumab received it every 4 weeks (99%; n = 572). Changes in dose frequency were rare for both agents (Supplementary Table 2).

Stopping BTA treatment was more common in patients receiving ZA (18%; n = 106/591) than in those receiving denosumab (8%; n = 47) (Fig. 1). A total of 81 patients discontinued BTAs (14%) and 24% (n = 25) switched to another BTA, with most (88%; n = 22) receiving denosumab as their second BTA. A total of 41 patients discontinued BTAs (7%) and 13% (n = 6) switched to another BTA; most of these (67%; n = 4) were prescribed ZA as a second BTA. The main reasons for discontinuing ZA among those who did not then receive a second BTA (n = 81) were: end of planned treatment with ZA (19%; n = 15); decreased renal function (14%; n = 11); risk of osteonecrosis of the jaw (ONJ) (12%; n = 10); presence of ONJ (10%; n = 8); and primary tumor progression (10%; n = 8). Among patients who discontinued denosumab and did not receive a second BTA (n = 41), the main reasons for discontinuation were: presence of hypocalcemia (22%; n = 9); lack of compliance as perceived by the physician (15%; n = 6); primary tumor progression (12%; n = 5); risk of ONJ (10%; n = 4); and patient's request (10%; n = 4).

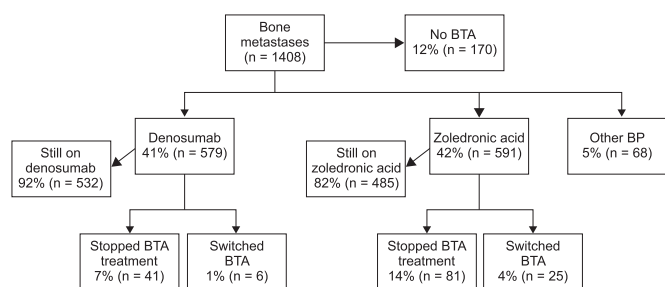


Fig. 1. BTA treatment flow for patients with advanced breast cancer and bone metastases. BP, bisphosphonate; BTA, bone-targeted agent.

**Table 2**  
Top four reasons given by physicians for initiating BTA treatment early ( $\leq 3$  months) following BM diagnosis.

n (%)	Overall (N = 1003)	Belgium (n = 82)	France (n = 229)	Germany (n = 201)	Italy (n = 130)	Spain (n = 179)	UK (n = 182)
Bone pain	336 (33)	32 (39)	70 (31)	73 (36)	57 (44)	45 (25)	59 (32)
High risk of bone complications	313 (31)	39 (48)	63 (28)	57 (28)	29 (22)	70 (39)	55 (30)
Number of BMs	130 (13)	8 (10)	37 (16)	17 (8)	16 (12)	20 (11)	32 (18)
Location of BMs	82 (8)	1 (1)	30 (13)	18 (9)	10 (8)	17 (9)	6 (3)

Physicians were asked to rank up to three reasons from a predefined list. High risk of bone complications was determined as per the treating physician's clinical opinion. Bone complications included pathologic fracture, spinal cord compression, bone radiation, and bone surgery. BM, bone metastases; BTA, bone-targeted agent.

**4.4. Patient pain and analgesic use**

Data collected from the PRFs showed that at the time of BM diagnosis, 79% (n = 1117) of patients were experiencing bone pain (Table 4). A larger proportion of patients who were considered at high risk of bone complications (defined as pathologic fracture, spinal cord compression, bone radiation, or bone surgery; n = 665) experienced moderate to severe pain than those considered at low risk of bone complications (n = 210) (49% vs 25%, respectively). There was an overall significant effect of the distribution of bone pain severity between the two patient risk groups ( $p < 0.001$ ). Of the 1408 patients with BMs, 14% (n = 194) had experienced a bone complication at the time of BM diagnosis. Of these patients, 78% (n = 152) experienced moderate to severe bone pain, as assessed by physicians. There were 1214 patients who did not have a bone complication at BM diagnosis; of these, 38% (n = 462) experienced moderate to severe bone pain.

At the time of data collection (mean of 11.2 months after BM diagnosis), 68% (n = 958) of patients were experiencing bone pain, with 20% experiencing moderate to severe pain (Table 4). Almost all of these patients, 97% (n = 927), were taking analgesics to manage this pain, including 42% (n = 398) who were taking non-opioid analgesics and 28% (n = 266) who were receiving strong opioids (Table 5). Trends in analgesic use were broadly similar across the countries studied, with the exception of Belgium where the use of non-opioid analgesics was more common than in the other countries.

Of the 927 patients receiving analgesics, the majority (89%; n = 829) were receiving or had received a BTA. Analgesic use was broadly similar between those who had received a BTA and those who had not (data not shown); however, a significantly higher proportion of those who had never received a BTA required non-opioid analgesics only compared with those who had received a BTA (53% vs. 42%;  $p = 0.03$ ).

**4.5. Patient-reported outcomes**

Of the 1408 patients with BMs, 392 completed a PSCF, and of the

**Table 3**  
Top four reasons given by physicians for delaying initiation of BTA treatment ( $> 3$  months) following BM diagnosis.

n (%)	Overall (N = 235)	Belgium (n = 7)	France (n = 50)	Germany (n = 17)	Italy (n = 46)	Spain (n = 85)	UK (n = 30)
Very recent diagnosis, so not had time to initiate	55 (23)	–	8 (16)	4 (24)	4 (9)	33 (39)	6 (20)
Low risk of bone complications	35 (15)	2 (29)	10 (20)	1 (6)	6 (13)	9 (11)	7 (23)
Patient refusal	21 (9)	3 (43)	7 (14)	3 (18)	2 (4)	1 (1)	5 (17)
Risk of ONJ	18 (8)	–	8 (16)	2 (12)	6 (13)	2 (2)	–

Physicians were asked to rank up to three reasons from a predefined list. Low risk of bone complications was determined as per the treating physician's clinical opinion. Bone complications included pathologic fracture, spinal cord compression, bone radiation, and bone surgery. BM, bone metastases; BTA, bone-targeted agent; ONJ, osteonecrosis of the jaw.

**Table 4**  
Pain levels in patients with BMs.

	All patients with BMs (N = 1408)	Perceived risk of bone complications		Previous bone complication	
		Low (n = 210)	High (n = 665)	No (n = 1214)	Yes (n = 194)
Bone pain at time of bone metastases diagnosis, n (%)					
No	279 (20)	67 (32)	113 (17)	270 (22)	9 (5)
Mild pain	503 (36)	86 (41)	219 (33)	471 (39)	32 (16)
Moderate pain	457 (32)	42 (20)	233 (35)	382 (31)	75 (39)
Severe pain	157 (11)	11 (5)	93 (14)	80 (7)	77 (40)
Unknown	12 (1)	4 (2)	7 (1)	11 (1)	1 (1)
	All patients with BMs (N = 1408)	Perceived risk of bone complications		Current bone complication	
		Low (n = 210)	High (n = 665)	No (n = 70)	Yes (n = 888)
Bone pain at time of data collection, n (%)					
No	445 (32)	78 (37)	200 (30)	0 (0)	0 (0)
Mild pain	665 (47)	97 (46)	333 (50)	26 (37)	639 (72)
Moderate pain	259 (18)	30 (14)	126 (19)	31 (44)	228 (26)
Severe pain	34 (2)	5 (2)	6 (1)	13 (19)	21 (2)
Unknown	5 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Bone complications were defined as pathologic fracture, spinal cord compression, bone radiation, or bone surgery. Perceived risk of bone complications was assessed at the time of first treatment decision. BMs, bone metastases.

1136 patients with non-BMs, 374 completed a PSCF. Baseline demographic and clinical characteristics of patients who completed a PSCF are shown in Table 6. The common metastatic sites for patients with non-BMs were liver (n = 249), lung (n = 197), and lymph nodes (n = 107). None of these patients had lymph node only metastases.

**Table 5**  
Use of analgesic medications in patients with advanced breast cancer and BMs reporting bone pain.

AQA score, n (%)	Overall (N = 958)	Belgium (n = 60)	France (n = 212)	Germany (n = 166)	Italy (n = 158)	Spain (n = 196)	UK (n = 166)
0 = no analgesics	31 (3)	3 (5)	5 (2)	12 (7)	8 (5)	1 (1)	2 (1)
1 = non-opioid analgesics	398 (42)	42 (70)	85 (40)	69 (42)	47 (30)	99 (51)	56 (34)
2 = weak opioids <sup>a</sup>	263 (27)	6 (10)	60 (28)	42 (25)	43 (27)	52 (27)	60 (36)
3 = strong opioids (75 mg OME/day)	187 (20)	5 (8)	44 (21)	29 (17)	38 (24)	33 (17)	38 (23)
4 = strong opioids (> 75–150 mg OME/day)	59 (6)	4 (7)	14 (7)	9 (5)	16 (10)	10 (5)	6 (4)
5 = strong opioids (> 150–300 mg OME/day)	18 (2)	0 (0)	3 (1)	5 (3)	6 (4)	0 (0)	4 (2)
6 = strong opioids (> 300–600 mg OME/day)	2 (< 0.5)	0 (0)	1 (0.5)	0 (0)	0 (0)	1 (1)	0 (0)

<sup>a</sup> For example, codeine and tramadol. AQA, Analgesic Quantification Algorithm; BMs, bone metastases; OME, oral morphine equivalent.

**Table 6**  
Patient demographics and clinical characteristics for patients with metastases who completed a patient self-completion form.

	BMs (n = 392)	Non-BMs (n = 374)
Age, mean (SD), for those aged < 90 years	63.5 (11.8)	62.9 (11.0)
Number of patients aged > 90 years	1	2
Age, median (25–75th percentiles)	64 (56–72)	63 (57–70)
Postmenopausal, n (%)	330 (86)	325 (87)
Family history of breast or ovarian cancer, n (%)	49 (12)	24 (6)
Time since breast cancer diagnosis, months, median (25–75th percentiles)	12.3 (3.4–39.7)	10.9 (3.0–26.7)
Number of comorbidities, mean (SD)	1.11 (1.46)	0.78 (1.06)

BMs, bone metastases; non-BMs, metastases at sites other than bone; SD, standard deviation.

Overall, patients with BMs had worse outcomes in terms of QoL, pain, and function than patients with non-BMs based upon a univariate Mann-Whitney analysis (Table 7). Using the BPI, patients with BMs scored pain at its worst, on average, and interference overall significantly higher than those with non-BMs. Mean BPI scores for patients with BMs were generally aligned with physician-reported severity categories of current bone pain (Supplementary Table 3). The EQ-5D overall index and EQ-VAS scores showed that patients with BMs perceived their health status as being significantly worse than those with non-BMs. In the FACT-B overall and domain scores, the trend was for lower mean scores for patients with BMs than for those with non-BMs, although significance was reached only for the physical well-being domain (Table 7).

A multivariable linear regression analysis was performed on all of these results to account for confounding factors (age, smoking status, time since diagnosis of breast cancer positive ER status, positive HER2 status, and number of comorbidities), which confirmed the trends seen in univariate analysis in terms of worse QoL, worse overall health, worse pain, and worse function for patients with BMs compared with those with non-BMs (Fig. 2).

Comparing pain outcomes in patients with BMs using the BPI revealed that patients who were receiving a BTA (n = 331) reported significantly lower average (95% CI) pain severity scores (2.7 [2.49–2.91] vs. 3.5 [2.93–4.07]; p = 0.004) and interference scores (3.2 [2.96–3.44] vs. 3.8 [3.16–4.44]; p = 0.036) than those who did not receive a BTA (n = 55).

## 5. Discussion

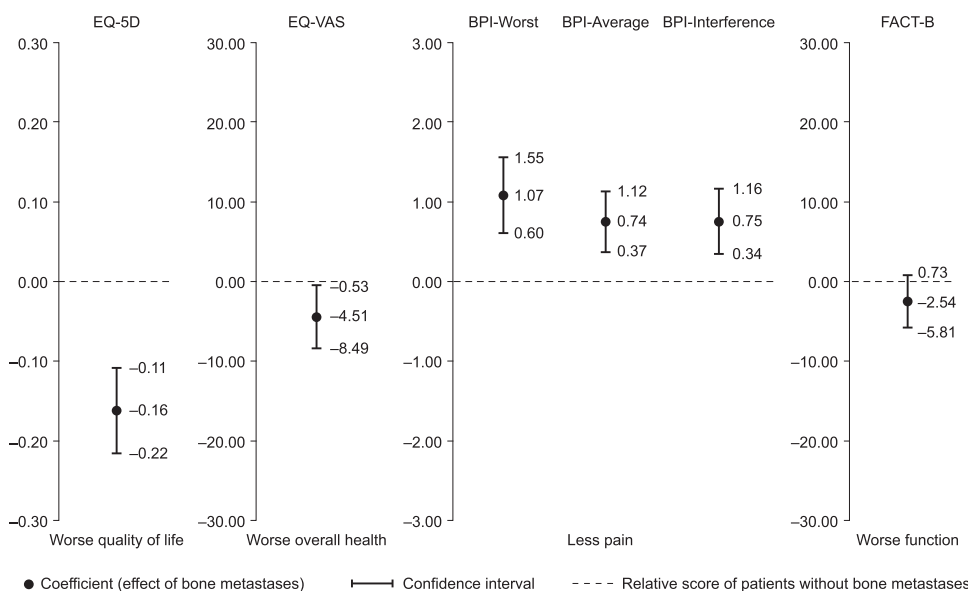
This multi-country, cross-sectional study revealed important data on real-world BTA treatment patterns and PROs in patients with advanced breast cancer. Encouragingly, most patients (88%) with BMs were treated with BTAs. Moreover, most of these patients received treatment

**Table 7**  
Patient-reported outcomes in patients with BMs compared with patients with non-BMs: univariate Mann-Whitney tests.

Response category	BMs	Non-BMs	p value
<b>BPI score, mean (95% CI)</b>	n = 389	n = 373	
Worst	3.7 (3.5–4.0)	2.7 (2.5–2.9)	< 0.001
Average	2.8 (2.6–3.0)	2.1 (1.9–2.2)	< 0.001
Interference	3.3 (3.0–3.5)	2.5 (2.3–2.7)	< 0.001
<b>EQ-5D</b>	n = 386	n = 368	
EQ-5D, mean (95% CI) overall index score	0.64 (0.61–0.68)	0.8 (0.78–0.83)	< 0.001
<b>Mobility, n (%)</b>	n = 389	n = 373	
No problems	214 (55)	273 (73)	< 0.001
Some problems	159 (41)	94 (25)	
Confined to bed	16 (4)	6 (2)	
<b>Self-care, n (%)</b>	n = 390	n = 373	
No problems	272 (70)	298 (80)	0.001
Some problems	106 (27)	69 (19)	
Unable to wash or dress self	12 (3)	6 (2)	
<b>Usual care activities, n (%)</b>	n = 390	n = 373	
No problems	181 (46)	242 (65)	< 0.001
Some problems	177 (45)	123 (33)	
Unable to perform usual activities	32 (8)	8 (2)	
<b>Pain/discomfort, n (%)</b>	n = 389	n = 371	
No pain	126 (32)	204 (55)	0.057
Moderate pain	231 (59)	158 (43)	
Extreme pain	32 (8)	9 (2)	
<b>Anxiety/depression, n (%)</b>	n = 388	n = 371	
No anxiety/depression	145 (37)	169 (46)	0.003
Moderate anxiety/depression	191 (49)	177 (48)	
Extreme anxiety/depression	52 (13)	25 (7)	
<b>EQ-VAS, mean (95% CI) overall index score</b>	58.8 (56.7–60.9)	63.9 (61.7–66.0)	< 0.001
<b>FACT-B, mean (95% CI)</b>	n = 374	n = 359	
Overall score	83.8 (81.7–85.9)	86.4 (84.5–88.3)	0.107
Physical well-being	17.9 (17.3–18.5)	19.3 (18.7–19.8)	0.001
Social well-being	17.3 (16.7–17.8)	17.3 (16.7–17.9)	0.955
Emotional well-being	12.8 (12.3–13.3)	13.1 (12.6–13.6)	0.293
Functional well-being	12.0 (11.4–12.5)	12.4 (11.9–13.0)	0.305
Additional concerns	24.0 (23.4–24.6)	24.6 (24.0–25.1)	0.262
Trial outcome index	53.8 (52.4–55.3)	56.2 (54.9–57.5)	0.030
<b>FACT-G, mean (95% CI)</b>	n = 374	n = 359	
Overall score	59.9 (58.3–61.5)	61.8 (60.2–63.3)	0.140

EQ-5D scores may vary between –0.59 (worst health) and 1.00 (perfect health). The EQ-VAS indicates patients' overall self-perceived health state, with a scale ranging from 0 to 100 (0 is the worst imaginable health state; 100 is the best imaginable health state). BPI pain severity was based on pain at its worst and average, with score ranging from 0 (no pain) to 10 (pain as bad as can be imagined). Pain interference scores ranged from 0 (does not interfere) to 10 (completely interfere). The FACT-B assessment is specific to breast cancer patients and comprises of six domains: physical well-being, social/family well-being, relationship with doctor, emotional well-being, functional well-being, and additional concerns. Lower scores indicate worse function. BMs, bone metastases; BPI, Brief Pain Inventory; CI, confidence interval; EQ-5D, 5-dimension EuroQol questionnaire; EQ-VAS, EuroQol visual analog scale; FACT-B, Functional Assessment of Cancer Therapy – Breast questionnaire; FACT-G, Functional Assessment of Cancer Therapy – General questionnaire.





**Fig. 2.** Patient-reported outcomes in patients with bone metastases compared with patients with non-bone metastases: multivariate linear regression analyses. Error bars show 95% confidence intervals. Mean values are presented. EQ-5D scores may vary between -0.59 (worst health) and 1.00 (perfect health). The EQ-VAS indicates patients' overall self-perceived health state, with a scale ranging from 0 to 100 (0 is the worst imaginable health state; 100 is the best imaginable health state). BPI pain severity was based on pain at its worst and average, with score ranging from 0 (no pain) to 10 (pain as bad as can be imagined). Pain interference scores ranged from 0 (does not interfere) to 10 (completely interfere). The FACT-B assessment is specific to breast cancer patients and comprises of six domains: physical well-being, social/family well-being, relationship with doctor, emotional well-being, functional well-being, and additional concerns. Lower scores indicate worse function. BPI, Brief Pain Inventory; EQ-5D, 5-dimension EuroQol questionnaire; EQ-VAS, EuroQol visual analog scale; FACT-B, Functional Assessment of Cancer Therapy – Breast questionnaire.

during the 3 months following BM diagnosis. The number of patients treated with BTAs was higher than the approximately 60% previously reported in a large US population study of more than 10,000 patients with breast cancer [28]. This may reflect selection bias in favor of this study, because physicians agreeing to participate were likely to be aware of the prevalence of BMs and SREs and the importance of treating patients. Alternatively, the high BTA treatment rate reported here may reflect improvements in the real-world management of bone disease; a similarly high rate of BTA treatment was reported in a recent chart audit of BTA use in five European countries (EU5; France, Germany, Italy, Spain, and the UK) of patients with BMs from solid tumors, in which 68% of patients received a BTA [29]. Further improvements in the treatment of individuals with BMs might be expected considering recent updates to guidelines such as the European Society for Medical Oncology (ESMO) clinical practice guidelines, which recommend initiating BTAs as soon as BMs are diagnosed [30,31]. Nonetheless, continued physician education on the importance of early initiation and maintenance of BTAs is required to ensure optimum patient care.

Nearly 20% of patients with BMs either experienced a delay in receiving BTA treatment or received no BTA treatment. The main reasons physicians gave for not initiating treatment were that the diagnosis of BMs was recent, patients were at a perceived low risk of bone complications, or they had a short life expectancy. These data are in line with those from the recent EU5 chart audit in which short life expectancy was also given as one of the main reasons for not prescribing BTAs, despite most patients in this group having a moderate to high estimated risk of developing an SRE, because a large proportion had received radiation to bone and/or had experienced a pathologic fracture (as evaluated by the physician) [29]. Furthermore, over two-thirds of these patients were expected to live for more than 1 year (as evaluated by the physician) [29]. Considering that the mean time from diagnosis of metastatic bone disease to developing an SRE is only a few months [6], patients with life expectancies of 6 months or less can still benefit from treatment. Furthermore, given the difficulties in accurately predicting life expectancy [32], a number of patients who could benefit from BTA treatment may remain untreated.

A high or low perceived risk of bone complications was frequently cited as one of the main reasons for treating or not treating patients with BTAs, respectively. A number of factors have been associated with an increased risk of SREs, including: increased age (patients aged ≥60 years have a higher SRE risk than younger patients); osteoporosis; elevated levels of the bone turnover markers urine N-telopeptide of type I collagen and bone-specific alkaline phosphatase; elevated levels of

lactate dehydrogenase; bone-only metastatic disease; large bone lesion size; predominance of osteolytic lesions; multiple bone lesions; presence of moderate to severe bone pain; and a previous SRE [33–38]. In this study, bone complication risk was determined by the investigator using their clinical judgement. *Post hoc* analyses revealed that patients who were perceived by their physician to have a high risk of bone complications were more likely than those with a low risk to have BMs in the vertebrae or at multiple skeletal locations and to be experiencing moderate to severe pain at BM diagnosis. Although it is recommended that all patients receive a BTA following BM diagnosis, this study shows that perceived SRE risk influences physicians' treatment decisions. Improved awareness among physicians of the prevalence of SREs in untreated patients and the associated pain and morbidity would help to standardize BTA treatment patterns, ensuring that all patients receive appropriate treatment, particularly because in real-world practice there is no commonly used definition of low versus high bone complication risk. Indeed, there is an unmet need for a predictive tool to ascertain the risk of first and subsequent SREs.

Efficacy and safety were the main motivating factors for physicians when selecting a BTA for their patients. As such, ZA and denosumab were the most commonly prescribed BTAs. Both agents were frequently given at their recommended dose (every 3–4 weeks for ZA and every 4 weeks for denosumab) and changes in dosing frequency were rare for both agents. Recent data show that ZA every 12 weeks is non-inferior to ZA every 4 weeks for the prevention of SREs and for delaying pain progression in patients with BMs from solid tumors; however, reduced dosing frequency was not associated with reduced toxicity [39]. Although the numbers of patients prescribed ZA and denosumab were equivalent, twice the proportion of patients taking ZA discontinued treatment compared with those discontinuing denosumab. Reasons for discontinuation differed between the two agents, but included concerns regarding renal impairment (ZA only), hypocalcemia, and ONJ. Of note, some data have shown that the incidence of SREs was two times higher in patients receiving a non-recommended dosing schedule compared with those receiving the recommended schedule [40]; although recent findings from an open-label study have shown no significant difference in the incidence of SREs between dosing schedules [39].

Renal insufficiency is a common comorbidity in patients with BMs [41]. ZA should not be used in patients with severe renal impairment and serum creatinine should be monitored in all patients receiving ZA; dose adjustments may be necessary if renal function deteriorates on treatment [17]. In contrast, routine renal monitoring is not required

with denosumab and no dose adjustment is needed in patients with renal impairment [18]. ONJ and hypocalcemia are rare but potentially serious events in patients receiving BTAs [42–44]. For both, preventative measures and regular monitoring should be undertaken so that patients can continue to receive BTA treatment [17,18].

Most patients (79%) had bone pain at diagnosis of BM and bone pain was a main reason for initiating BTA treatment. This is consistent with previous data showing that BMs are frequently diagnosed as a result of bone pain; in a chart audit of patients with breast cancer who were receiving BTAs, more than half of women presented with bone pain at BM diagnosis [38]. This has consequences for the management of BMs and bone pain because evidence suggests that early detection and treatment of BMs, before the onset of pain, could provide patients with greater pain palliation and protection from SREs [45,46]. The recent EU5 chart audit of BTA use in patients with BMs identified differences between countries in the detection of BMs [29]. In patients with solid tumors, BMs were diagnosed in more than one-third as a result of bone pain. This was not the case in Germany, where BMs were diagnosed in 20% of patients as a result of bone pain; routine screening during follow-up was the main method of BM detection (41%) [29]. Furthermore, data from our study showed that, compared with patients from the other five countries studied, patients in Belgium had a shorter time from breast cancer diagnosis to BM diagnosis, and received BTAs soon afterwards; quite possibly as a result of this, patients were less likely to require strong opioid pain medication. This suggests that improved detection methods and guidelines for BM diagnoses are required to support early diagnosis and treatment. A recent meta-analysis has suggested that BTAs have greatest impact on bone pain by delaying its onset, rather than having an analgesic effect per se [47]. Early detection of BMs using routine screening could therefore be worthwhile for patients with a high-risk of bone complications because this has the potential to prolong symptom-free duration, which patients have rated as being one of the most important treatment goals [48].

Previous data has shown that severe bone pain occurs in around 75% of patients suffering from BMs from breast cancer [49]. Inadequate management of bone pain in patients with cancer is common, and has been reported to occur in up to 55% of those with advanced cancer [21,50,51]. In this study, most patients with BMs who reported current pain were taking analgesics, with 42% taking non-opioid analgesics and over one-quarter taking strong opioids. Despite this, 20% of these patients were currently experiencing moderate to severe pain, as reported by their physician. Interestingly, of the 392 patients with BMs who completed a PSCF, 68% reported that they were experiencing moderate to extreme pain (as per the EQ-5D definition). Although, in this study, mean BPI scores and the physician-reported severity categories of current bone pain were aligned, within the wider population there could be disparity between physicians' perception and patients' experience of pain. This may, in part, lead to under-treatment by physicians and inadequate pain management for patients. Patients with BMs who were not receiving a BTA reported worse pain scores than patients with BMs who were receiving a BTA, emphasizing the role BTAs play in managing bone pain; indeed a discrete choice experiment has shown that preventing pain worsening is a key consideration for patients when selecting a BTA [48].

Patients with BMs reported significantly worse pain and pain interference compared with those with non-BMs. Time without moderate or severe pain has been associated with increased functionality [52], confirming the importance of appropriate pain management. Indeed, patients with BMs reported significantly worse health statuses compared with those with non-BMs; EQ-5D scores showed that from approximately one-quarter to one-half of patients with BMs had 'some problems' for each of the domains of mobility, self-care, usual care activities, pain/discomfort, and anxiety/depression. Several organizations have recently published guidelines on the management of cancer pain [45,53,54]; however, further physician education may be required to raise awareness of patient pain and to ensure that current guidelines

are reflected in real-world clinical practice.

This study had some limitations. First, data were self-reported by physicians and patients, and as such, no measures were clinically verified. Secondly, results of this study may have been biased by physician selection because physicians who were more aware of the issues related to BMs and SREs may have been more likely to participate in this study. The study design did, however, benefit from the fact that the Adelphi DSP is a recognized and consistent methodology that can be applied across multiple countries, enabling valid comparisons to be made. Additionally, because no tests or investigations were undertaken as part of the research, treatment decisions were unbiased and can be assumed to reflect real-world practice.

## 6. Conclusion

Patients with breast cancer and BMs have worse outcomes in terms of pain and QoL than those with breast cancer and non-BMs. Among patients with BMs, those treated with BTAs reported lower pain scores than those not treated with BTAs. Encouragingly, the majority of patients with breast cancer and BMs are treated with BTAs; however, there remains an educational need for physicians to ensure that BTAs are initiated early because the greatest benefit is in preventing pain and complications. Patient factors, such as risk of bone complications and life expectancy, influence physicians' BTA treatment decisions. Given the difficulties in accurately predicting these risks, further guidelines are required to support physicians in making BTA treatment decisions and to improve understanding of the consequences for patients who do not receive treatment or who stop treatment early.

## 7. Declarations

### 7.1. Ethics approval and consent to participate

The DSP adheres to Good Pharmacoepidemiology Practice (GPP) and the European Pharmaceutical Market Research Association (EphMRA) code of conduct. The EphMRA Code of Conduct states that research that meets the definition relating to market or consumer behaviour of the sort that pharmaceutical companies routinely commission, whether involving healthcare professionals, patients, carers or members of the public does not require Clinical Research Ethics Committee or Independent Review Board approval.

All data collection from the DSP is undertaken through third party fieldwork agencies, ensuring that the identity of healthcare professionals and patients is not known to Adelphi or any subscribers to the data. Furthermore, data are analyzed and provided to subscribers in an aggregated format. The EphMRA Code of Conduct states that once all identifiers linking data to the subject have been removed, it is anonymised and is no longer personal data and, therefore, not covered by the European Union Data Protection Directive. Patients who participated in the study provided consent for their self-completion data to be used by selecting a check box on the PSCF and by returning the PSCF for use. Physicians provided written consent for their data to be used via the online survey they completed. Physicians were paid a fair market rate for their time involved in completing the survey.

### 7.2. Consent for publication

Not applicable.

### 7.3. Availability of data and material

The data that support the findings of this study are available from Adelphi Real World but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Adelphi Real World.

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## Conflicts of interest

R. von Moos has received research grants from Amgen and Bayer, has consulted for Amgen, Bayer, Bristol Myers Squibb, GlaxoSmithKline, MSD, Roche, and Novartis, and has received honoraria from Amgen, Bayer, and GlaxoSmithKline.

J. J. Body has received lecture and consulting fees from Amgen.

A. Rider and J. de Courcy are employees of Adelphi Real World.

D. Bhowmik, F. Gatta, G. Hechmati and Y. Qian are employees of Amgen and own stock.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.jbo.2017.11.004>.

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