Symptomatic skeletal events and the use of bone health agents in a real-world treated metastatic castration resistant prostate cancer population: results from the CAPRI-study in the Netherlands

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**Clinical trial identification:** The CAPRI study is registered in the Dutch Trial Registry as NL3440 (NTR3591).
Abstract

Background: Patients with metastatic castration resistant prostate cancer (mCRPC) are at risk of symptomatic skeletal events (SSE). Bone health agents (BHA, i.e. bisphosphonates and denosumab) and new life-prolonging drugs (LPDs) can delay SSEs. The aim of this study is to investigate the use of BHAs in relation to SSEs in treated real-world mCRPC population.

Methods: We included patients from the CAPRI registry who were treated with at least one LPD and diagnosed with bone metastases prior to the start of first LPD (LPD1). Outcomes were SSEs (external beam radiation therapy (EBRT) to the bone, orthopaedic surgery, pathological fracture or spinal cord compression) and SSE-free survival (SSE-FS) since LPD1.

Results: 1,923 patients were included with a median follow-up from LPD1 of 16.7 months. Fifty-two percent (n=996) started BHA prior or within four weeks after the start of LPD1 (early BHA). In total, 41% experienced at least one SSE. SSE incidence rate was 0.29 per patient year for patients without BHA and 0.27 for patients with early BHA. Median SSE-FS from LPD1 was 12.9 months. SSE-FS was longer in patients who started BHA early vs patients without BHA (13.2 vs 11.0 months, p=0.001).

Conclusion: In a real-world population we observed an undertreatment with BHAs, although patients with early BHA use had lower incidence rates of SSEs and longer SSE-FS. This finding was irrespective of type of SSE and presence of risk factors. In addition to LPD treatment, timely initiation of BHAs is recommended in bone metastatic CRPC-patients with both pain and/or opioid use and prior SSE.
Introduction

Bone metastases occur in approximately 90% of patients with (metastatic) castration resistant prostate cancer (mCRPC)[1]. Bone health in mCRPC is further affected by the loss of bone mineral density due to ADT and higher age[2,3]. The result is ineffective haematopoiesis, bone pain and skeletal related events (SREs) which can lead to significant deterioration in quality of life and worsened survival[1,4–7].

SREs, defined as pathologic fractures, spinal cord compression, and the need for surgery or external beam radiation (EBRT) to relieve bone pain, occur in 40-50% of all mCRPC-patients[8–11]. Asymptomatic SREs are not considered clinically relevant, thus symptomatic skeletal events (SSE) have been proposed as an important new trial end point[12,13].

New life-prolonging drugs (LPD, i.e. docetaxel, cabazitaxel, abiraterone acetate plus prednisone, enzalutamide and radium-223 dichloride) have been registered for the treatment of mCRPC based on a survival benefit compared to mitoxantrone or placebo[14], but abiraterone acetate plus prednisone (AA+P), enzalutamide (ENZ) and radium-223 (Ra-223) have also shown a prolongation in time to first SRE[15–17].

Bone health agents (BHAs) prevent SREs without improving survival. Patients treated with zoledronic acid were less likely to experience an SRE than placebo treated patients (38% vs 49%)[10,11]. Denosumab, a monoclonal antibody, reduced the incidence of SREs to a greater extent than zoledronic acid (36% vs 41% with any SRE, respectively), but hypocalcaemia was more common (13% vs 6%, respectively)[18].

The optimal management of patients with bone metastatic CRPC remains unclear due to a lack of comparative data and low generalizability of trials results to daily practice[19]. Treatment decisions are highly variable and based on personal clinical judgement[20]. There seems however a general undertreatment with BHAs in bone metastatic CRPC patients. The number of patients with concomitant BHA use in the ERA-223 trial was low (41%) possibly explaining the high rate of mostly osteoporotic fractures in the combination arm (AA+P plus Ra-223)[21]. This increased the awareness of bone health in these patients. The objective of our study is to investigate the use and outcomes of BHAs in a treated real-world mCRPC cohort.

Methods
Study design and setting

CAPRI (CAstration-resistant Prostate cancer RegIstry) is an investigator-initiated, observational multicentre cohort study in 20 Dutch hospitals (11 large teaching hospitals, 5 general hospitals and 4 academic hospitals). The study design has been described before[19]. The study was approved by a central medical ethics committee and hospital board before the start of inclusion. The study is registered in the Dutch Trial Registry as NL3440 (NTR3591).

Participants

Patients diagnosed with CRPC were included in CAPRI retrospectively from January 1, 2010 until December 31, 2015. CRPC was either defined by the criteria set by the European Association of Urology (EAU)[14] or defined by the treating physician. All data have been regularly updated until December 31, 2017. Patients treated with at least one LPD for mCRPC and diagnosed with bone metastases before the start of first LPD (LPD1) were included in this analysis.

We identified groups based on timing of BHA. Patients without BHA use during follow-up were classified as “no BHA”, while “early BHA” was defined as start of BHA prior to or within four weeks after the start LPD1 and “late BHA” as the start of BHA after four weeks after the start of LPD1.

Follow-up and data collection

Predefined and readily available data from medical records were retrospectively collected by trained data managers in an electronic case report form (eCRF), and included all radiotherapy, hospital admissions, operations and treatment given (including LPD, radionuclides and BHA). The eCRF was updated in 2016 to allow for structural registration of spinal cord compression and pathologic fractures. These types of SSEs were derived from hospital admission reasons before 2016. Baseline characteristics were included if they were documented six weeks prior to one week after the start of new systemic treatment. All patients were followed until death, lost-to-follow-up or December 31st, 2017.

Outcome

Outcomes were clinically relevant skeletal complications: SSEs and SSE-free survival (SSE-FS). SSEs were defined as the occurrence of either external beam radiotherapy to the bone (EBRT), symptomatic pathological fractures, spinal cord compression or surgery to the bone. All SSEs were clinically detected and there was no
protocol mandated routine radiological assessment. All SSEs were calculated during total follow-up defined as period from LPD1 to end of follow-up.

SSE-FS was defined as time in months from first occurrence of SSE to death. Patients without an event (either death or SSE) were censored at last recorded date.

Statistical analysis
Descriptive statistics were performed. Missing baseline characteristics were imputed using multiple imputations with Monte Carlo Markov Chain method. Binary logistic regression was performed on pooled data after multiple imputation to assess the effect of baseline variables on SSE incidence. Kaplan-Meier analysis was used to estimate SSE-FS. A p-value of 0.05 or less was considered statistically significant. IBM SPSS Statistics Version 24.0 (IBM ©, Armonk, NY, USA) was used for all analyses.

Results
In total, 3,616 patients were included in the CAPRI registry, of which 2,540 (70%) had bone metastases and 2,274 (63%) were treated with an LPD. Patients with known bone metastases and ≥1 LPD treatment were included in the analyses (n=1,923; 53%). Median follow-up from LPD1 was 16.7 months (range 0-86 months).

Baseline characteristics
Baseline characteristics at the start of LPD1 are listed in Table 1. Median age was 73 years (range 46-99 years) and 62% (n=1,194) had an ECOG performance score of 0-1. Thirty-nine percent (n=746) had pain and/or used opioids. Median ALP was 157 U/L (IQR 99-335 U/L) and PSA 110.0 µg/L (IQR 43-264 µg/L). Twenty-seven percent (n=519) experienced at least one SSE prior to LPD1.

Treatment characteristics
The median time from CRPC diagnosis to LPD1 was 6.9 months (IQR 2-16 months). In total 717 patients (37%) were treated with 1 LPD, 589 (31%) with 2 LPDs, 617 (32%) with 3 or more LPDs. AA+P and ENZ were most commonly used (52% and 46% respectively).
Sixty percent (n=1,158) used BHA during follow-up, mostly zoledronic acid (n=626, 33%) or denosumab (n=276, 14%). Fifty-two percent (996/1,923) start BHA prior or within 4 weeks after the start of LPD1 (Table 2).

Patients who started BHA early were younger than patients without BHA (73 vs 75 years) and more frequently experienced a prior SSE (31% vs 22%) (Supplementary Table 1). Patients with late BHA use were the youngest (71 years) and had less frequently a ECOG PS ≥2 (5% vs 14% in patients with no BHA and 11% in patients without BHA, p=0.018).

**Symptomatic skeletal events**

SSE and SSE-FS was evaluable in 1,866 patients (97%): 717 (38%) without BHA, 976 (52%) with early BHA and 162 (9%) with late BHA. Forty-three percent (n=797) experienced one or more SSEs after the start of LPD1, mostly EBRT to the bone (41%) followed by spinal cord compression (6%), pathologic fracture (3%) and orthopaedic surgery (3%). The incidence of SSE was 0.26 per patient year for the total population (Table 2), 0.29 and 0.27 for patients without BHA and with early BHA use respectively (p=0.331) (Figure 1). The incidence rate for each type of SSE was lower in patients with early BHA compared to no BHA or late BHA, but only statistically significant for orthopaedic surgery and pathologic fractures (Figure 1).

At database cut-off, 1,340 patients (70%) had died, 244 (13%) were still alive and 339 patients (17%) were lost-to-follow-up. Median SSE-FS was 12.9 months (IQR 6-24 months). Patients with late BHA use were excluded from time-to-event analyses due to immortal time bias. SSE-FS was slightly longer in patients who started BHA early vs patients without BHA (13.2 vs 11.0 months, p=0.001) (Table 3; Figure 2).

**Subgroup analysis**

After correction for known prognostic factors, the presence of pain and/or opioid use at the start of LPD1 (OR 1.42, 95% CI 1.08-1.86, p=0.01) and an SSE prior to LPD1 (OR 4.00, 95% CI 3.16-5.07, p<0.01) were strong predictors for development of an SSE (Supplementary Table 2). We have created subgroups based on the presence of none (subgroup 1), one (subgroup 2) or both (subgroup 3) of these characteristics. BHA early use was the highest in patients with the highest risk (i.e. subgroup 3), namely 60.8% compared to 48.8% in subgroup 1 and 53.8% in subgroup 2 (p=0.044). Although early BHA use, 28% in subgroup 1, 49% in subgroup 2 and 65% in subgroup 3 experienced at least one SSE during follow-up (p<0.001).
The SSE incidence rate per patient year increased per subgroup: 0.18 in subgroup 1, 0.32 in subgroup 2, and 0.49 in subgroup 3 (p<0.001). Patients with early BHA use had lower SSE incidence rate per patient year compared to patients without BHA use in all subgroups, which was only statically significant in subgroup 3 (Figure 3).

SSE-FS was better for patients in subgroup 1 and 2 than patients in subgroup 3 (16.3 and 10.4 vs 6.9 months respectively, p<0.001). Patients with early use of BHA had longer SSE-FS than patients without BHA in subgroup 2 and 3 (12.1 vs 8.7 months, p=0.001 and 7.2 vs 5.9 months, p=0.033 respectively; Figure 4B and 4C), but not subgroup 1 (16.6 vs 15.9 months, p=0.307; Figure 4A).

**Discussion**

In this cohort analysis, we report SSEs in a real-world mCRPC population treated with LPDs. To our knowledge, this is the largest multicentre population without strict patient selection criteria in which patients are treated according to the views and opinions of their treating physicians. Outcomes therefore reflect current daily practice. Moreover, we used SSEs as an outcome which is clinically more relevant than SREs that also include asymptomatic skeletal events found on radiologic assessment.

All patients in this real-world mCRPC population were at risk for SSEs due to the presence of bone metastases and the prolonged use of ADT[2]. Forty-one percent actually experienced at least one SSE during follow-up, which was on the high end of previously reported rates ranging between 29% to 44%[10,22]. Patients who started BHAs early (prior or within the first month after the start of LPD1) had a lower incidence rate of SSEs and longer SSE-FS compared to patients without BHA use. Phase III trials have shown the effect of bisphosphonates (zoledronic acid) and denosumab on SREs and both prolong the time to first on-study SRE (20.7 months for denosumab and 17.1 months for zoledronic acid)[23]. This effect was similar when using only symptomatic events (i.e SSEs) as an endpoint[24]. Results from trials performed in selected patients are in general not easily generalizable to clinical practice, but in addition to our findings a recently published paper of 625 real-world CRPC-patients showed a reduction in SSE incidence rate with concomitant BHA use (0.34 vs 0.37 in with and without concomitant BHA respectively)[25].

Although both randomized trials and real-world evidence support the beneficial effect of BHAs and the guidelines promote the use of BHAs in all bone-metastatic CRPC-patients, only 60% of our population was treated with BHAs during follow-up[14,26–28]. This undertreatment is not new and similar to the 40-55% of
patients with concurrent BHA in similar populations[21,25]. The reasons not to start a BHA were not included in our database, but an European analysis reported that clinicians mainly withhold BHA treatment since they wanted to wait until first line LPD had failed or they estimated that the risk of bone complications was low[29]. The LPDs AA+P, ENZ and Ra-223 prolong the time to first SRE with approximately 3-6 months compared to placebo[15–17,30]. However, post-hoc analyses of these pivotal trials have shown an additional effect (i.e. longer OS, longer time to opiate use, and longer time to deterioration in ECOG PS) of combining LPDs with BHA[31,32].

We also investigated which patients can benefit from BHAs based on their risk of SSEs. Although other studies report elevated ALP, visceral metastases, Gleason score ≥7 and short interval between the initiation of ADT and CRPC diagnosis as risk factors, we have found that only patients with a prior SSE and with pain and/or opioid use were at higher risk of developing an SSE[33–35]. Patients who had either a prior SSE or pain and/or opioid use (or both) benefited the most from early BHA use. However, patients without these two characteristics who started BHA early also had a lower SSE incidence per patient year, although SSE-FS was not different from patients without BHA use. Our observation further supports timely initiation of BHAs (prior or early after the start of LPD1) in patients with bone metastases, especially in patients with a prior SSE or pain and/or opioid use (or both). Based on our data we were not able to determine optimal timing and duration of BHA.

The most common SSE was EBRT which can offer an adequate treatment for bone pain with an overall pain response in ranging from 66% to 84%[36,37]. Since bone pain is frequent and severe in mCRPC patients especially later disease phases, this could explain the high need for EBRT for symptom management[38]. Patients who started BHAs early had lower incidence rates of EBRT and also of other SSEs, but the incidence of other SSEs was low in our population (<10%). Our results on spinal cord compressions are similar to other studies, but we observed less pathologic fractures (3% vs 25%)[39]. We only captured symptomatic skeletal complications (SSEs) and not SREs which also include asymptomatic fractures on protocol mandated radiologic assessment. Changing the definition from SREs to SSEs mainly impacts the prevalence of pathologic fractures[24]. A phase III namely showed that the rate of pathologic fractures was 17% when the end point was SREs compared to 2% when the end point was SSEs[24].

In addition to SSEs which are more clinically relevant than SREs, SSE-FS offers a new clinical trial end point combining survival and SSEs into a single outcome. This provides an objective measurement of clinically meaningful benefit. The ERA-223 trial also used SSE-FS as an endpoint[21]. The ERA-223 trial included
asymptomatic or minimally symptomatic mCRPC patients with bone metastases randomized between AA+P with placebo or Ra-223 and after a median follow-up of 21.2 months, SSE-FS was 26.0 and 22.3 months, respectively[21]. In our cohort, median SSE-free survival was 12.9 months. The difference in SSE-FS in our observation can be explained by a high prevalence of SSEs compared to other studies [16,17,33,35,40]. We only included real-world patients who tend to have worse prognostic features than trial populations and thus are likely to have shorter SSE-FS.

The limitation of our study was the high number of missing values on baseline characteristics. This reflects incomplete evaluation of patients or lack of structured reporting in daily practice. High number of missing values leads to exclusion of many patients in multiple regression analysis, however imputation of missing baseline data offers a valid solution. Moreover, we miss data that might be of influence on the risk of SSEs (e.g. site of metastasis and metastatic burden). Residual confounding could therefore still be present in multivariable analysis.

We were not able to determine if skeletal complications occurred at a tumour site and information to discriminate with osteoporotic complications as serum levels of vitamin D or calcium and dual energy X-ray absorptiometry (DEXA) scans were not available in this study. Discriminating between tumour-related or osteoporotic complications is necessary, since they need different treatment strategies.

In this real-world analysis 41% of bone metastatic CRPC patients experienced an SSE during follow-up, even though all were treated with at least one LPD. Patients who started BHA early had lower incidence rate of SSEs and longer SSE-FS, irrespective of risk factors (prior SSE or pain and/or opioid use) and type of SSE. However, we found a possible undertreatment of BHAs since only 52% started BHA early. This warrants timely combining LPDs with BHAs in all bone metastatic CRPC-patients, but especially in patients with risk factors. Further prospective research should provide information about the optimal timing and duration of BHAs, especially in light of the availability of new LPDs.

**Clinical practice points**

- Patients with metastatic castration resistant prostate cancer (mCRPC) are prone to symptomatic skeletal events (SSEs) due to bone metastases and suboptimal bone health caused by higher age and use of androgen deprivation therapy. Both new life-prolonging drugs (LPD, e.g. abiraterone acetate plus prednisone, enzalutamide and radium-223) as well as bone health agents (BHAs, e.g. zoledronic acid and
denosumab) prevent skeletal related events. Optimal management of bone metastatic CRPC remains challenging due to a lack of comparative data and low generalizability to daily practice.

- We investigated the use and outcomes of BHAs in bone metastatic CRPC-patients treated with one or more LPDs between 2010 and 2019 in the real-world CAPRI registry. In patients who started BHA early (52% of 1,923 patients) SSE incidence was lower and SSE-free survival was longer. This was irrespective of the type of SSE and of the presence of risk factors.

- These results show that timely initiation of BHA in mCRPC-patients treated with LPDs is recommended due to lower SSE incidence, especially in patients with risk factors (i.e. pain and/or opioid use and prior SSE). Future prospective research should indicate optimal timing of BHAs, especially in light of changing treatment patterns.

**Conflict of interest**

M.C.P. Kuppen has received travel/accommodation expenses from Ipsen; H.M. Westgeest has received travel/accommodation expenses from Ipsen and honoraria from Roche; A.J.M. van den Eertwegh has received study grants from Sanofi and Roche, travel expenses from MSD Oncology, Roche, Pfizer and Sanofi, honoraria from Bristol-Myers Squibb, and is a member of the advisory board of Bristol-Myers Squibb, MSD Oncology, Amgen, Roche, Novartis, Sanofi, Pfizer, Ipsen and Merck; R.J.A. van Moorselaar has received honoraria/consultation fees of Astellas, AstraZeneca, Bayer, Janssen and Sanofi-Genzyme; I.M. van Oort has received study grants from Astellas, Janssen and Bayer, and has a consulting/advisory role for Astellas, Janssen, Bayer, Roche, Mdx health; M. Tascilar has no conflict of interest; N. Mehra has received study grants from Astellas, Janssen, Pfizer, Roche and Sanofi Genzyme, has a consulting/advisory role for Roche, MSD, BMS, Bayer, Astellas and Janssen, and has received travel/accommodation expenses from Astellas and MSD; J. Lavalaye has no conflict of interest; D.M. Somford has received study grants from Astellas and honoraria from Astellas and Janssen; K.K.H. Aben has no conflict of interest; A.M. Bergman has received study grants from Sanofi, Astellas and Bayer, travel/accommodation expenses from Sanofi, Astellas and Bayer, speakers fees of Sanofi, Astellas, Bayer and Janssen, and has an consulting/advisory role for Sanofi, Astellas and Bayer;
R. de Wit has a consulting/advisory role for Sanofi, Merck Sharp&Dohme, Roche/Genentech, Janssen, Bayer and Clives, has received honoraria from Sanofi and Merck Sharp&Dohme and study grants from Sanofi and Bayer.

A.C.M. van den Bergh has no conflict of interest; C.A. Uyl-de Groot has received study grants from Boehringer Ingelheim, Astellas, Celgene, Sanofi, Janssen-Cilag, Bayer, Amgen, Genzyme, Merck, Glycostem Therapeutics, Astra Zeneca and Roche; W.R. Gerritsen has received speaker’s fees from Bayer and MSD, study grants from Bayer, Astellas and Janssen-Cilag, and is a member of the advisory board of Bristol-Myers Squibb, Astellas, Bayer, Sanofi, and Amgen.
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Legends of figures

Figure 1 SSE incidence rate per patient year. * statistically significant differences (p<0.05).

Abbreviations: SSE, symptomatic skeletal events; BHA, bone health agents; EBRT, external beam radiation therapy.
Figure 2 SSE-FS based on BHA use. Abbreviations: BHA, bone health agents; SSE-FS, symptomatic skeletal event free survival.
Figure 3 SSE incidence rate per patient year per subgroup * statistically significant differences (p<0.05).

Subgroup 1 i.e. patients without pain and/or opioid use and without prior SSE; Subgroup 2 i.e. patients with only pain and/or opioid use or only prior SSE; subgroup 3 i.e. patients with both pain and/or opioid use and prior SSE. **Abbreviations:** SSE, symptomatic skeletal events; BHA, bone health agents; EBRT, external beam radiation therapy.
Figure 4 SSE-FS based on BHA use per subgroup (A) patients without pain and/or opioid use and without prior SSE (subgroup 1); (B) patients with only pain and/or opioid use or only prior SSE (subgroup 2); (C) patients with both pain and/or opioid use and prior SSE (subgroup 3). Abbreviations: BHA, bone health agents; SSE-FS, symptomatic skeletal event free survival.
Table 1 Baseline characteristics at the start of LPD1

| Parameter                                      | Total N=1,923 |
|------------------------------------------------|---------------|
| **Age (years)**                                |               |
| median (range)                                 | 73 (46-99)    |
| ≥ 75 years (n, %)                              | 869 (45)      |
| ECOG PS, n (%)                                 |               |
| 0                                              | 390 (20)      |
| 1                                              | 804 (42)      |
| ≥2                                             | 224 (12)      |
| unknown                                       | 505 (26)      |
| Charlson comorbidity index, n (%)              |               |
| 0                                              | 1,258 (65)    |
| 1-2                                            | 557 (29)      |
| 3-4                                            | 88 (5)        |
| > 4                                            | 20 (1)        |
| unknown                                       | 0 (0)         |
| Pain and/or opioid use, n (%)                  |               |
| yes                                           | 746 (39)      |
| no                                            | 222 (12)      |
| unknown                                       | 955 (50)      |
| Visceral metastases, n (%)                     |               |
| yes                                           | 223 (12)      |
| no                                            | 811 (42)      |
| unknown                                       | 889 (46)      |
| Time ADT to mCRPC (mo)                         | median (IQR)  |
| unknown, n (%)                                 | 13.1 (8-24)   |
| Time ADT to LPD1 (mo)                          | median (IQR)  |
| unknown, n (%)                                 | 22.4 (13-41)  |
| Hb (mmol/L)                                    | median (IQR)  |
| unknown, n (%)                                 | 7.8 (7.0-8.4) |
| LDH (U/L)                                      | median (IQR)  |
| unknown, n (%)                                 | 237 (193-328) |
| ALP (U/L)                                      | median (IQR)  |
| unknown, n (%)                                 | 157 (99-335)  |
| PSA (µg/L)                                     | median (IQR)  |
| unknown, n (%)                                 | 110 (43-264)  |
| SSE prior to LPD1, n (%)                       |               |
| yes                                           | 519 (27)      |
| no                                            | 1,211 (63)    |
| unknown                                       | 193 (10)      |

All baseline parameters are measured in the period 6 weeks prior to 1 week after the start of LPD1. Total percentages can exceed 100% due to rounding.

*Abbreviations: LPD, life-prolonging drug; ECOG PS, Eastern Cooperative Group Performance Score; ADT,*
androgen deprivation therapy; mCRPC, metastatic castration resistant prostate cancer; mo, months; Hb, hemoglobin; IQR, interquartile range; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; PSA, prostate specific antigen; SSE, symptomatic skeletal event.

### Table 2 Treatments characteristics

| Life prolonging drugs | Total |
|-----------------------|-------|
|                       | N=1,923 |

#### Life prolonging drugs

| Number of LPDs during follow-up, n (%) | 1 | 2  | 3  | >3 |
|---------------------------------------|---|----|----|----|
| 717 (37)                              | 589 (31) | 393 (20) | 224 (12) |

| Type of LPDs, n (%) | docetaxel | cabazitaxel | abiraterone acetate plus P | enzalutamide | radium-223 |
|---------------------|-----------|-------------|---------------------------|--------------|-----------|
| 575 (30)            | 415 (22)  | 992 (52)    | 885 (46)                  | 272 (14)     |

| Time from mCRPC diagnosis to first LPD (mo) | median | IQR |
|---------------------------------------------|-------|-----|
|                                             | 6.9   | 2-16|

#### Bone health agents

| BHA during follow-up, n (%) | no | yes | unknown |
|-----------------------------|----|-----|---------|
|                             | 750 (39) | 1,158 (60) | 15 (1) |

| Type of BHA, n (%) | zoledronic acid | other bisphosphonates<sup>a</sup> | denosumab | combination<sup>b</sup> | unknown |
|-------------------|-----------------|----------------------------------|-----------|--------------------------|---------|
|                   | 626 (33)        | 161 (8)                          | 276 (14)  | 90 (5)                   | 5 (<1)  |

| Time to BHA, n (%) | early use<sup>a</sup> | use after LPD1 |
|--------------------|------------------------|---------------|
|                    | 996 (52)               | 162 (8)      |

Total percentages can exceed 100% due to rounding.

<sup>a</sup> other includes pamidronic acid (n=95), alendronic acid (n=53), risedronic acid (n=7), clodronic acid (n=3), unknown bisphosphonates (n=3);
<sup>b</sup> switch between bisphosphonates and denosumab during follow-up;
<sup>c</sup> start of BHA prior to or within four weeks after the start of LPD1.

**Abbreviations:** LPD, life-prolonging drug; mo, months; IQR, interquartile range; BHA, bone health agents.

### Table 3 Symptomatic skeletal events during follow-up

| Total |
|-------|
| N=1,866 |
# Table 1: SSE during Follow-up and SSE-Free Survival

| Event Description                  | SSE Total | EBRT Bone | Orthopedic Surgery | Spinal Cord Compression | Pathologic Fracture |
|------------------------------------|-----------|-----------|--------------------|-------------------------|---------------------|
| SSE during follow-up, n (%)        | 797 (43)  | 759 (41)  | 57 (3)             | 112 (6)                 | 64 (3)              |
| Number of SSEs, n (%)              |           |           |                    |                         |                     |
| 1                                  | 617 (33)  |           |                    |                         |                     |
| 2                                  | 150 (8)   |           |                    |                         |                     |
| ≥3                                 | 30 (2)    |           |                    |                         |                     |
| SSE-FS (mo) median (IQR)           | 12.9 (6-24)|          |                    |                         |                     |
| Event SSE, n (%)                   | 797 (43)  |           |                    |                         |                     |
| Event death, n (%)                 | 721 (39)  |           |                    |                         |                     |
| Censored, n (%)                    | 348 (19)  |           |                    |                         |                     |
| All person-time (years)            | 2.935     |           |                    |                         |                     |
| SSE, n per patient year            |           |           |                    |                         |                     |
| SSE total                          | 0.27      |           |                    |                         |                     |
| EBRT bone                          | 0.26      |           |                    |                         |                     |
| Orthopedic surgery                 | 0.02      |           |                    |                         |                     |
| Spinal cord compression            | 0.04      |           |                    |                         |                     |
| Pathologic fracture                | 0.02      |           |                    |                         |                     |

Total percentages can exceed 100% due to rounding.

**Abbreviations:** IQR, interquartile range; BHA, bone health agents; SSE, symptomatic skeletal events; EBRT, external beam radiation therapy; SSE-FS, SSE-free survival.