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Uptake of bone modifying agents in patients with HER2+ metastatic breast cancer with bone metastases – prospective data from a multi-site Australian registry.

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Declaration

This work is not under active consideration for publication, has not been accepted for publication, nor has it been published, in full or in part (except in abstract form). I confirm that the study has been approved by Melbourne Health HREC, an institutional ethics committee.

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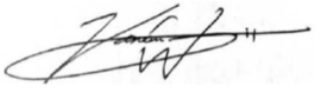

Dr Vanessa Wong
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Conflicts of Interest

Vanessa Wong's affiliated institution is the recipient of research grant funding from Pierre-Fabre, Amgen, Novartis, Roche and Merck (all for unrelated activities)

Richard de Boer has received honorarium from Novartis, Amgen, Roche, AstraZeneca, Eli Lilly and Genomic Health. He has received travel expenses from Novartis and Amgen (all for unrelated activities).

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Belinda Yeo has been part of Novartis, Amgen, Genetech/Roche and AstraZeneca Advisory Board. She has received speaker fees from Roche, Novartis, Eisai, Myriad and Specialised Therapeutics, as well as travel grants from Roche and Novartis (all for unrelated activities)

Peter Gibbs has received research grants from Pierre-Fabre, honorarium from Roche, consulting fees and lecture payments from MSD, Merck and Amgen (all for unrelated activities)

Sheau Wen Lok's affiliated institution is the recipient of research grant funding from Novartis, Astra Zeneca, Roche and Amgen (all for unrelated activities).

Laeeq Malik, Sally Greenberg, Frances Barnett, Michelle Nottage, Louise Nott, Ian M Collins, Javier Torres, Catherine Dunn declare they have no conflicts of interest that might be relevant to the contents of this manuscript.

ABSTRACT

Background and Aim

International practice guidelines recommend administration of bone modifying agents (BMA) in metastatic breast cancer (MBC) patients with bone metastases to reduce skeletal related events (SRE). Optimal delivery of BMA in routine clinical practice including agent selection and prescribing intervals remains unclear. We aim to describe real-world practice of Australian breast oncologists.

Methods

Prospective data from February 2015 to July 2020 on BMA delivery to MBC patients with bone metastases was analysed from TABITHA, a multi-site Australian HER2+ MBC registry.

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Results

Of 333 HER2+ MBC patients, 171 (51%) had bone metastases at diagnosis, with a mean age of 58.1 years [range 32-87]. 130 (76%) patients received a BMA, with 90 (69%) receiving denosumab and 40 (31%) receiving a bisphosphonate. Patients who received a BMA were more likely to have received concurrent first line systemic anti-HER2 therapy (95% vs 83%, p=0.04), to present with bone-only metastases at diagnosis (24% vs 7%, p=0.02) and less likely to have visceral metastases (51% vs 71%, p=0.03). Ten of 40 (25%) bisphosphonate patients and 45 of 90 (50%) denosumab patients received their BMA at the recommended 4-weekly interval. Prescribing intervals varied over time. Adverse events reported were consistent with clinical trial data.

Conclusion

Three-quarters of Australian HER2+ MBC patients with bone metastases receive a BMA, often at different schedules than guidelines recommend. Further studies, including of all MBC subtypes, are warranted to better understand clinicians' prescribing rationale and potential consequences of current prescribing practice on SRE incidence.

BACKGROUND

Bone metastases occur frequently in patients with solid tumours but are most prevalent in breast (65-70%), prostate (65-70%) and lung (30-40%) cancers (1). The use of bone modifying agents (BMAs), in the form of potent osteoclast inhibitors, has become an important component of managing patients with bone metastases. The two classes of agents used for osteoclast inhibition in patients with bone metastases are the bisphosphonates, for example zoledronic acid, and the Receptor Activator of Nuclear factor Kappa-B Ligand (RANKL) monoclonal antibodies, for example, denosumab (2). The aim of BMA use is to reduce the frequency of additional bone metastases, relieve bone pain and delay the onset of skeletal related events (SRE) defined as pathological fractures, need for radiation therapy or surgery to the bone, spinal cord compression and hypercalcaemia of malignancy.

International practice guidelines, including the recent ESMO publication of 'Bone Health in Cancer' (3), consistently recommend the use of BMAs for patients with metastatic breast cancer (MBC) with bone metastases (4,5). Whilst denosumab has demonstrated superiority over zoledronic acid in time to SRE (6), there was no survival advantage and thus, there is not a preferred agent due to 'insufficient evidence of a clinical meaningful benefit' of one agent over another (4,5). In Australia, both bisphosphonates (zoledronic acid and ibandronate) and the RANKL monoclonal antibody (denosumab) have been approved for use in patients with MBC and bone metastases. In landmark MBC clinical trials, zoledronic acid (dose 4mg intravenously) and denosumab (dose 120mg subcutaneously) have been administered every 4 weeks (7,8).

Randomised controlled trials exploring bisphosphonate treatment intervals in MBC patients, such as ZOOM(9) and OPTIMIZE-2(10) were ultimately underpowered to demonstrate non-inferiority of the less intensive schedules

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but did suggest that de-escalating zoledronic acid from a 4 weekly to a 12 weekly dosing interval (after 12-15 months at a 4 weekly interval) may be a clinically acceptable alternative. Subsequently, CALGB 70604 (11) which included patients with MBC, castrate resistant prostate cancer and multiple myeloma, randomised patients at initiation of zoledronic acid to 4-weekly or 12-weekly dosing intervals. This larger non-inferiority trial demonstrated that 12-weekly dosing of zoledronic acid was not associated with higher rates of overall SRE when compared with 4-weekly dosing in the first two years of follow up, but there was a greater proportion of patients requiring surgical treatment with the longer dosing interval. Given that follow-up for all 3 trials was relatively short (1-2 years) and uncertainty persists regarding the higher rate of more serious SRE, recent guidelines have advised an initial 4-weekly treatment for 3-6 months, prior to de-escalating to 12 weekly treatment (3).

In addition, the evidence to date for de-escalation appears to be more robust for zoledronic acid as compared to denosumab (12-13). This is largely due to the differing pharmacokinetics; zoledronic acid as a bisphosphonate accumulates in the bone and thus has a long skeletal half-life whereas denosumab as a RANKL antibody is not incorporated into bone, and this argues against intermittent dosing intervals for denosumab. (14-16).

Despite trial evidence, the BMA prescribing preferences of Australian clinicians in routine clinical care has not been well defined, and little is known about the justification for choice of agent, timing of initiation, dose, schedule, monitoring of bone health and incidence of adverse effects. Given the prevalence of bone metastases in MBC patients, and the lack of consensus on many issues surrounding use of BMAs, we aimed to improve our understanding in the variation of use in routine clinical practice.

METHODS

The Treatment of Advanced Breast Cancer in the HER2 Positive Australian patient (TABITHA) registry was established in 2015 as a collaboration between clinicians at Walter and Eliza Hall Institute and BioGrid Australia with funding from a pharmaceutical industry sponsor. This is a prospective multi-centre initiative collecting data on patient characteristics, disease presentation, treatment patterns and outcomes of patients with HER2 positive MBC treated in routine care at 16 sites across Australia. Data collected includes management of bone metastases and bone health, such as DEXA scans and vitamin D and calcium prescription. Data on consecutive metastatic HER2+ breast cancer patients with bone metastases between February 2015 to July 2020 were analysed. This study and its reporting have been approved by Melbourne Health HREC, an institutional ethics committee.

The primary objective of the current study was to understand prescribing patterns of BMA in real world practice, by describing selection of agent, timing of initiation and treatment intervals. Secondary objectives include comparing clinical characteristics between patients who received BMA and those that did not, documented reasons for non-initiation of BMA, receipt of radiation for bone metastases, uptake of bone health interventions and incidence of BMA adverse effects, namely hypocalcaemia and osteonecrosis of the jaw. We did not explore the impact of BMA use on the rate of SRE, given that SRE data was not captured prospectively and our sample

size would also be too small to support any robust conclusions given the very mixed patient population receiving and not receiving a BMA. SAS® Enterprise Guide® and GraphPad Prism 8 version software was used to analyse the data. Fisher's exact test was used to determine statistical significance for categorical data, one-sample Wilcoxon signed rank test was used to compare between non-Gaussian continuous data and paired t tests for Gaussian continuous data. Overall survival and progression-free survival analyses used Kaplan-Meier methods. Statistical significance was reported when $p<0.05$.

RESULTS

Of 333 HER2+ MBC patients, 171 (51%) patients had bone metastases at the time of diagnosis of metastatic disease. Of these 130 (76%) received bone modifying agents (BMA) at some point in the treatment course (**Figure 1**)

Clinical characteristics of patients who received a bone modifying agent

Clinical characteristics comparing patients who did (n=130) and did not (n=41) receive a BMA are demonstrated in **Table 1**. Patients who received a BMA were more likely to have bone-only metastases at metastatic breast cancer diagnosis (24% vs 7%, p=0.02) and less likely to have presence of visceral metastases (51% vs 71%, p=0.03).

The 41 patients (24%) who did not receive a BMA were more likely to have not received any first line systemic chemotherapy (24% vs 10%, p=0.03) or any anti HER2+ treatment (17% vs 5%, p=0.04). For 15 of 41 (37%) patients who did not receive BMA, a justification was provided by the treating clinician and captured in the registry database. These were 'low volume disease' (n=7), 'poor performance status' (n=2), 'older age' (n=2), patient declined (n=2)', 'poor renal function' (n=1) and 'clinician decision' (n=1).

One in four patients with bone metastases received radiotherapy, with patients who received a BMA being more likely to receive radiation therapy for bone metastases (32% vs 12%, p=0.015).

Prescribing patterns of bone modifying agents

Of 130 patients who received BMAs, 121 (93%) were initiated at the time that first line systemic treatment was commenced after diagnosis of bone metastases. Seven were initiated during second line, and two were initiated during third line treatment. Of the nine patients starting after first line, three had documented reasons for delaying BMA commencement. These were: awaiting dental review' (n=1), 'refused dental extraction' (n=1) and 'mild osteopenia with no bone pain' (n=1).

With regard to BMA selection, 40 of 130 (31%) patients received bisphosphonates and 90 of 130 (69%) received denosumab. Initial treatment interval varied amongst selected agent, with overall 56 patients (43%) commencing a BMA at the trial defined 4-weekly schedule (**Table 2**).

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Figure 2 demonstrates subsequent BMA use post systemic disease progression on their initial agent. Of the 87 patients who progressed on first line systemic and initial BMA therapy, 62 (71%) developed progressive disease in the bone and 25 (29%) had progressive disease in non-bone sites. Of the 62 patients who had disease progression in the bone, either alone or with other sites, 37 (60%) continued on the same BMA, 6 (14%) switched BMA and 19 (31%) stopped their BMA. In comparison, of the 25 patients who had non-bone disease progression, 11 (40%) continued on same BMA, 1 (4%) switched BMA and 14 (56%) stopped their BMA. All patients who switched bone therapy were initially prescribed bisphosphonate and switched to denosumab upon progression. Notably, no patients switched from denosumab to bisphosphonate upon progression.

There was a trend that patients with progressive disease in the bone were more likely to continue on some form of BMA beyond first line, as compared to those with non-bone progressive disease sites (69% vs 48%, p= 0.06). Additionally, of the 33 patients that ceased BMA use, 20 (61%) also ceased all systemic HER2 directed treatment.

For patients who continued to receive a BMA post systemic disease progression, subsequent treatment interval continued to vary as graphically demonstrated in the Sankey diagram in Figure 3.

Management of bone health

Documented tools used to assess bone health included dual energy X-ray absorptiometry (DEXA) scans and serum bone turnover markers (total procollagen type 1 N-terminal propeptide – P1NP, crosslinked C-telopeptide – CTX). For the 130 patients who received a BMA, 45 (35%) had DEXA scans and 9 (7%) had urinary bone turnover markers.

Additional interventions for bone health for those receiving BMA were reported. Of the 130 patients, 13 (10%) were documented to have received Vitamin D supplements, 57 (44%) received calcium supplements, 9 (7%) received documented advice on weight bearing exercises.

Treatment complications of bone modifying agents

Specific treatment complications of hypocalcaemia and osteonecrosis of the jaw were prospectively collected (Table 3).

DISCUSSION

To our knowledge, this is the first study to delineate Australian clinicians' prescription of BMAs in patients with HER2+ MBC with bone metastases. Whilst denosumab appears to be favoured by clinicians over bisphosphonates, and the majority of patients were initiated on a BMA at the time of diagnosis of bone metastases, one in four

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HER2+ MBC patients with bone metastases did not receive a BMA at any point in their treatment course. In addition, there was significant variation reported in BMA treatment intervals both at time of initiation and thereafter.

The proportion of MBC patients not receiving a BMA has varied from 4% to 45% in routine practice in studies from the United States of America and Europe (17-21). Unlike previous studies which have reported that elderly breast cancer patients were less likely to receive BMA (17,22), we did not observe an age difference between patients who received BMA as compared to those that did not. McGrath et al (17) reported in an American cohort that patients were less likely to receive a BMA if they had non-bone metastases. Similarly, in our Australian cohort, of those that did not receive a BMA, there was a lower proportion of patients with bone-only metastases, and a higher proportion of patients with visceral metastases. The prioritisation of systemic chemotherapy or HER-2 directed therapy in context of visceral disease may be a potential explanation for this finding, with clinicians electing to withhold BMA, for fear of adding complexity to the existing systemic treatments. Other reasons could include low perceived risk of bone complications or wanting to wait until first-line systemic treatment has failed before initiating a BMA (23).

Conversely, a significant proportion of patients who did not receive a BMA also did not receive any systemic therapy (either anti-HER2 agents or chemotherapy). This is likely to reflect a cohort of patients who, whether through preference or performance status, are unsuited for systemic anticancer treatment and are treated with best supportive care (BSC) alone. Whilst the primary analgesic role of BMA in the management in acute bone metastases is unclear, palliative care guidelines advocate for use of long-term BMA treatment in combination with analgesia, to delay onset of malignant bone pain (24-26). However, mandatory prescribing of BMA to patients with a poor overall prognosis needs to be carefully considered as it may be burdensome both to patients and health systems, with limited clinical or symptomatic benefit to the patient. Short life expectancy was given as one of the main reasons for not prescribing BMAs for MBC in a cross-sectional European physician survey (27). The Cochrane meta-analysis on BMAs and breast cancer demonstrate that despite BMAs reducing the overall absolute risk of SRE by 14-22%, there is only a modest improvement in bone pain for BMA in isolation, with quality-of-life scores only slightly better and the difference in scores decreasing during course of studies (28). Studies comparing bisphosphonates to placebo have demonstrated that it can take 3 months on treatment to report a definitive reduction in SRE in the bisphosphonate arm (6,7) and thus a proportion of patients on a BSC pathway may not survive to receive this benefit. Further research is warranted on the optimal selection of patients that will benefit most from BMA in the BSC setting.

The most common documented reason for non-initiation of BMA was low burden of bone metastases. Whilst there is no clinically validated algorithm to predict which MBC patients with bone metastases will develop an SRE, previous studies suggest that SRE often occurs early, at a median time of 2 months from initial diagnosis (8). Given that the initial landmark BMA studies in breast cancer demonstrated a delay in the median time to the occurrence

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of the first SRE by almost 50%, patients are recommended to start BMAs from first radiological confirmation of bone metastases, regardless of the presence of symptoms (3,29).

Denosumab was favoured over bisphosphonates in our study. Potential explanations for this preference may be the convenience of subcutaneous administration of denosumab, or the reported superiority of denosumab in delaying SREs compared with the intravenous bisphosphonates (6,8,16). However, despite the landmark trials utilising 4-weekly administration of BMA, the majority of patients in our registry were not initially prescribed a BMA at this treatment interval. This was especially true of patients commencing a bisphosphonate, where only 25% commenced on a 4-weekly schedule. It is important to note that our data was obtained from a HER2+ MBC registry, where HER2+ directed agents are commonly given at 3-weekly schedules, which may explain why 50% of bisphosphonate patients and 32% of denosumab patients received their BMA at a 6-weekly interval. It is likely then that clinicians' BMA selection of prescribing interval is largely dependent on the convenience of coinciding administration with scheduled visits for systemic therapy. A study from United States on multiple myeloma patients (30), reported that patients had better adherence to BMA when this coincided with anti-myeloma systemic therapy administered at the same dosing schedule.

Moreover, as BMAs have not been demonstrated to impact on overall survival, clinicians may be more comfortable with varying dosing intervals and duration from guidelines. A survey of Canadian oncologists reported that the most common prescribing intervals were denosumab 4-weekly for 3-4 months followed by de-escalation to 12-weekly for patients with MBC, with the majority of clinicians uncertain of the benefit of continuing BMA therapy after 2 years (31). In contrast, a Swiss survey of uptake of BMA in all solid tumour types found that only 8% of oncologists de-escalated to 12-weekly after the first 3 months, and only 1 in 3 de-escalating to 12-weekly interval after 2 years (32).

Another key concern is the perceived cost-effectiveness of BMA balanced with the health and financial burden of SRE. Extending dosing intervals, choice of BMA or planned cessation are potential solutions to help decrease the overall drug cost on national healthcare benefit schemes. Shapiro et al (33) performed a cost-effectiveness analysis comparing 3 monthly zoledronic acid versus monthly denosumab in a retrospective observational study from a US payer perspective, concluding that generic zoledronic acid every 3 months was more cost effective in reducing the risks of SRE than monthly denosumab. When evaluating the number needed to treat (NNT), 7 patients would have to be treated with a bisphosphonate to avoid one more patient developing a SRE (28). When comparing 4-weekly zoledronic acid to 4-weekly denosumab, 18 patients would have to be treated with denosumab as an alternative to zoledronic acid for 34 months to avoid one more patient developing an SRE, with NNT of 27 to avoid radiation therapy to bone, and NNT of 39 to avoid pathologic fracture (8, 34). However, this may be offset by longer time to SRE and ease of access with subcutaneous delivery. Likewise, there are marked variables on the financial burden of SRE, include the location of bone metastases, type of SRE, hospitalisation costs and need for surgery or radiation therapy (35). Further research is required to help delineate the cost-

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effectiveness of BMA in an Australian setting, coupled with ongoing research identifying a subset of patients that would benefit from de-escalation of dosing intervals and early BMA cessation.

Whilst guidelines have supported a de-escalation of zoledronic acid treatment intervals to 12-weekly, after initial 4-weekly dosing for 3-6 months (3), de-escalation of denosumab treatment interval is less clear. The recently published ReACT BTA trial reported non-inferiority in health-related quality of life and physical functioning between 4-weekly and 12-weekly dosing intervals of both bisphosphonates and denosumab from prescribing onset for patients with MBC or castrate resistant prostate cancer (36). Results from the prospective phase 3 randomised controlled trial, SAKK 96/12 REDUSE study (Clinicaltrials.gov identifier: NCT0205128) comparing symptomatic SRE when de-escalating denosumab from 4-weekly to 12-weekly is eagerly awaited. However of concern, discontinuation of denosumab, when prescribed for osteoporosis or in the adjuvant breast cancer setting with the aim of decreasing skeletal metastases, has been associated with a small increase in spontaneous vertebral crush fractures and an increase in bone turnover markers, due to rapid rebound bone osteolysis (37-40). This risk has not yet been delineated in the metastatic setting, although guidelines recommend short-term bisphosphonate therapy in this setting to mitigate this risk (3).

The majority of patients continued to receive a BMA past first systemic progression, especially those who demonstrated bone-specific progressive disease. There were 7 patients who switched from bisphosphonate to denosumab and no patients switching from denosumab to bisphosphonates. Guidelines recommend that patients should remain on a BMA indefinitely unless contraindicated, with clinically significant benefits and with no significant increase in serious adverse events, however treatment interruption can occur in patients with good prognostic features such as oligometastatic disease and durable response to systemic treatment (3). With regards to switching BMA therapy post progressive skeletal metastases, there is a paucity of data to create guidelines and inform practice. Mjelstad et al (41) in a single centre retrospective cohort study of 255 patients with bone metastases (37% had breast cancer) demonstrated that switching from a bisphosphonate to denosumab after first SRE or skeletal disease progression was independently associated with longer time to SRE compared to continuation with the same bisphosphonate (HR 0.47, 95% CI 0.25-0.88, p=0.019). In addition, a phase 2 randomised controlled trial by Fizazi et al (16) enrolled 111 patients with bone metastases (41% had breast cancer) who were at high risk of SRE due to elevated urinary bone turnover markers receiving a bisphosphonate. Compared to patients remaining on a bisphosphonate, those that were randomised to switching to denosumab had a reduced incidence of SREs at 25 weeks (8% vs 17%, HR 0.31, 95% CI 0.08-1.18).

Our study demonstrated that there was a low proportion of patients who received tools used to monitor bone health. Whilst bone health monitoring, especially DEXA scans, is recommended for patients receiving BMA either for osteoporosis or to decrease risk of skeletal recurrence in the adjuvant breast cancer setting, the role of bone health monitoring tools in the MBC setting for management of bone metastases is not clearly defined. The uptake of additional interventions such as the prescription of Vitamin D in this cohort were lower than anticipated, as

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supplementation with calcium and vitamin D should be mandatory unless contraindicated. This likely reflects incomplete documentation in medical records.

BMA adverse effects of hypocalcaemia and osteonecrosis of the jaw were infrequently seen in patients on both bisphosphonates and on denosumab, consistent with clinical trial data (8). No atypical femoral fractures were reported, although this adverse effect was not listed as a data item and would have been captured as an 'other' event, maybe making it less likely to be documented. Notably, randomised clinical trials evaluated for BMA adverse events when the duration of BMAs was delivered for 1-2 years, even though in routine clinical practice, duration of BMA for patients with bone metastases is commonly administered beyond 2 years. A recent systematic review on patients reported an increase in incidence of osteonecrosis of the jaw, from 1-4% in the first 2 years to 3.8-18% beyond 2 years suggesting cumulative toxicity (42). Thus, whilst remaining on BMA does reduce risk of SRE, further studies are required to predict which patients would continue to symptomatically benefit to mitigate risk.

There are several limitations to our study. Data may not be representative of all Australian practice, and as for all registry studies, data may be incomplete. This is particularly true regarding the incidence of SRE which was not collected prospectively and is the reason that this important endpoint is not reported here. Data are also lacking on the specific duration of BMA treatment, as data recorded on BMA use was related on changes to overall systemic treatment and timepoints of cancer progression. Data on baseline factors that may have impacted on use of BMA in the MBC setting such as dental consideration, and prior use of BMA for management of osteoporosis or for risk reduction in high risk early breast cancer was not routinely collected. Moreover, clinician rationale for the initiation, timing of cessation and choice of BMA treatment interval was not specifically collected in the TABITHA registry and thus, only potential descriptive hypotheses can be inferred from our data. Additionally, our cohort only included HER2+ MBC patients, and thus overall real-world management of all Australian MBC patients (including hormone positive and triple negative) would require further research.

In conclusion, it is reassuring to see that three-quarters of Australian HER2+ MBC patients who fit guideline recommendations for BMA receive them in a timely manner, albeit for many at a different prescribing interval than recommended in international practice guidelines. Given these data, further studies are warranted to understand clinicians' reasons for not prescribing BMAs and any impact of this on patient outcomes, including SRE rates. The impact of the variable selection of BMA agent and dosing interval is unknown but indicates persistent clinician uncertainty as to the optimal initiation and continuation of these agents. As part of WEHI clinical comprehensive registries, the newly recruiting Advanced Hormone Receptor Positive Breast Cancer Registry in Australia (ARORA) aims to build on the results collected from this study with updated data fields to help better understand clinician decision making including the incidence and nature of skeletal related events.

REFERENCES

Author Manuscript

1. Macedo F, Ladeira K, Pinho F, Saraiva N, Bonito N, Pinto L et al. Bone Metastases: An Overview. Oncol Rev. 2017; 11(1): 321.

2. Heeke A, Nunes MR, Lynce F. Bone-Modifying Agents in Early-Stage and Advanced Breast Cancer. Curr Brast Cancer Rep. 2018; 10(4): 241–250.

3. Coleman R, Hadji P, Body JJ, Santini D, Chow E, Terpos E et al. Bone Health in Cancer: ESMO Clinical Practice Guidelines. Ann Oncol. 2020 Dec; 31(12):1650-1663

4. Van Poznak CV, Somerfield MR, Barlow WE, Biermann JS, Bosserman LD, Clemons MJ et al. Role of Bone-Modifying Agents in Metastatic Breast Cancer: An American Society of Clinical Oncology–Cancer Care Ontario Focused Guideline Update. J Clin Oncol. 2017; 35(35): 3978-3986.

5. Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, Andre F et al. 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). Ann Oncol. 2018;29(8): 1634-1657.

6. Lipton A, Fizazi K, Stopeck AT, Henry DH, Brown JE, Yardley DA et al. 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. 2012;48(16):3082–3092.

7. Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. Cancer. 2003;98(8):1735-1744.

8. Stopeck A, Lipton A, Body JJ, Steger GG, Tonkin K, de Boer RH et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol. 2010; 28(35): 5132-5139.

9. Amadori D, Aglietta M, Alessi B, Gianni L, Ibrahim T, Farina G et al. Efficacy and safety of 12-weekly versus 4-weekly zoledronic acid for prolonged treatment of patients with bone metastases from breast cancer (ZOOM): a phase 3, open-label, randomised, non-inferiority trial. Lancet Oncol. 2013;14(7):663-670.

10. Hortobagyi GN, Van Poznak CV, Harker WG, Gradishar WJ, Chew H, Dakhil SR et al. Continued Treatment Effect of Zoledronic Acid Dosing Every 12 vs 4 Weeks in Women With Breast Cancer Metastatic to Bone: The OPTIMIZE-2 Randomized Clinical Trial. JAMA Oncol. 2017;3(7), p.906.

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11. Himelstein AL, Foster JC, Khatcheressian JL, Roberts JD, Seisler DK, Novotny PJ et al. Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone Metastases: A Randomized Clinical Trial. JAMA. 2017 Jan 3;317(1):48-58.

12. Awan A, Paterson A, Clemons M. De-Escalation of Bone-Modifying Agents in Patients With Bone Metastases: The Best of Times and the Worst of Times? J Oncol Pract. 2018; 14(8):465-467

13. Luo Q, Men P, Liu Z, Zhai S, Jiang M. Is De-escalated Bisphosphonates Therapy a Suitable Alternative to Standard Dosing in Malignant Tumour Patients With Bone Metastases: A Systematic Review and Meta-Analysis. Front Oncol. 2019; 9:774.

14. Narayanan P. Denosumab: A comprehensive review. South Asian Journal of Cancer. 2017;2(4), 272–277.

15. Lipton A, Steger GG, Figueroa J, Alvarado C, Solal-Celigny P, Body JJ et al. Extended efficacy and safety of denosumab in breast cancer patients with bone metastases not receiving prior bisphosphonate therapy. Clin Cancer Res. 2008; 14(2):6690–6696.

16. Fizazi K, Lipton A, Mariette X, Body JJ, Rashim Y, Gralow JR et al. Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. J Clin Oncol. 2009;27(10):1564–1571.

17. McGrath LJ, Overman RA, Reams D, Cetin K, Liede A, Narod SA et al. Use of bone-modifying agents among breast cancer patients with bone metastasis: evidence from oncology practices in the US. Clin Epidemiol. 2018; 10: 1349-1358.

18. Schröder J, Fietz T, Köhler A, Peterson V, Tesch H, Spring L et al. 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. 2017;79: 139-148.

19. Arican A, Bozhurt T, Bozcuk H, Demirkan B, Buyukberber S, Alkis N et al. A cross-sectional survey of the diagnosis and management of bone metastasis in breast cancer patients in Turkey. Supportive Care in Cancer. 2014;22(10), 2629-2634.

20. Kuchuk I, Hutton B, Moretto P, Ng T, Addison CL, Clemons M. Incidence, consequences and treatment of bone metastases in breast cancer patients—Experience from a single cancer centre. Journal of Bone Oncology. 2013;2(4), 137-144.

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21. Murphy L, McCarthy J, McCrate F, Laing K, Powell E, Seal M et al. Use of bisphosphonates in metastatic breast cancer: single institution review at the Dr. H. Bliss Murphy Cancer Centre. Supportive Care in Cancer. 2013;21(6):1557-1560.

22. Giordano SH, Fang S, Duan Z, Kuo YF, Hortobagyi GN, Goodwin JS et al. Use of Intravenous Bisphosphonates in Older Women with Breast Cancer. The Oncologist. 2008; 13(5), 494-502

23. Body JJ, von Moos R, Rider A, Hallworth P, Bhowmik D, Gatta F et al. 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. 2018 Dec 18;14:100212.

24. Marr HK, Stiles CR, Boyar MA, Braun TC, Hagen NA, Janzen C et al. Feasibility of administering zoledronic acid in palliative patients being cared for in the community: results of a pilot study. Current Oncology. 2010; Apr;17(2):69-74.

25. Porta-Sales J, Garzón-Rodríguez C, Llorens-Torromé S, Brunelli C, Pigni A, Caraceni A. Evidence on the analgesic role of bisphosphonates and denosumab in the treatment of pain due to bone metastases: A systematic review within the European Association for Palliative Care guidelines project. Palliat Med. 2017 Jan;31(1):5-25.

26. Yoong J, Poon P. Principles of cancer pain management: An overview and focus on pharmacological and interventional strategies. Australian Journal of General Practice. 2018;Nov;47(11):758-762.

27. von Moos R, Body JJ, Rider A, de Courcy J, Bhowmik D, Gatta F et al. 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. 2017 Nov 24;11:1-9.

28. O'Carrigan B, Wong MH, Willson ML, Stockler MR, Pavlakis N, Goodwin A. Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev. 2017 Oct 30;10(10):CD003474.

29. D'Oronzo S, Coleman R, Brown J, Silvestris F. Metastatic bone disease: Pathogenesis and therapeutic options. Journal of Bone Oncology. 2018;15:004.

30. McGrath LJ, Hernandez RK, Overman R, Reams D, Liede A, Brookhart MA et al. Initiation and interruption in intravenous bisphosphonate therapy among patients with multiple myeloma in the United States. Cancer Medicine. 2019;8(1), 374-382.

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31. AlZahrani M, Clemons M, Vandermeer L, Sienkiewicz M, Awan AA, Hutton B, Pond GR, Ng TL. 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. 2020 Nov 10;26:100339.

32. Mark M, Thürlimann B, Ribi K, Schär C, Dietrich D, Cathomas R et al. Patterns of care for patients with metastatic bone disease in solid tumors: A cross-sectional study from Switzerland (SAKK 95/16). J Bone Oncol. 2019 Dec 16;21:100273.

33. Shapiro CL, Moriarty JP, Dusetzina S, Himelstein AL, Foster JC, Grubbs SS et al. Cost-Effectiveness Analysis of Monthly Zoledronic Acid, Zoledronic Acid Every 3 Months, and Monthly Denosumab in Women With Breast Cancer and Skeletal Metastases: CALGB 70604 (Alliance). J Clin Oncol. 2017 Dec 10;35(35):3949-3955.

34. Dranitsaris G, Hatzimichael E. Interpreting results from oncology clinical trials: a comparison of denosumab to zoledronic acid for the prevention of skeletal-related events in cancer patients. Support Care Cancer. 2012 Jul;20(7):1353-60.

35. Tella SH, Kommalapati A, Singhi RK. Cost-effectiveness in managing skeletal related events in breast cancer: a strategy of less-intense dosing schedule of bone modifying agents. Transl Cancer Res. 2018 Feb;7(Suppl 1):S81-S84.

36. Clemons M, Ong M, Stober C, Ernst S, Booth C, Canil C et al. A randomised trial of 4- versus 12-weekly administration of bone-targeted agents in patients with bone metastases from breast or castration-resistant prostate cancer. Eur J Cancer. 2021 Jan;142:132-140.

37. Anastasilakis, A., Polyzos, S., Makras, P., Aubry-Rozier B, Kaouri S, Lamy O. Clinical Features of 24 Patients With Rebound-Associated Vertebral Fractures After Denosumab Discontinuation: Systematic Review and Additional Cases. Journal of Bone and Mineral Research. 2017;32(6), pp.1291-1296.

38. Gonzalez-Rodriguez, E., Aubry-Rozier, B., Stoll, D, Zaman K, Lamy O. Sixty spontaneous vertebral fractures after denosumab discontinuation in 15 women with early-stage breast cancer under aromatase inhibitors. Breast Cancer Research and Treatment. 2019; 179(1), pp.153-159.

39. Lamy, O., Stoll, D., Aubry-Rozier, B. and Rodriguez, E. Stopping Denosumab. Current Osteoporosis Reports. 2019; 17(1), pp.8-15.

40. Gonzalez-Rodriguez, E., Aubry-Rozier, B., Stoll, D., Zaman K, Lamy O. Increased Risk of Multiple Spontaneous Vertebral Fractures at Denosumab Discontinuation Must Be Taken Into Account. Journal of Clinical Oncology. 2020;38(14), pp.1641-1642.

41. Mjelstad, A., Zakariasson, G. and Valachis, A. Optimizing antiresorptive treatment in patients with bone metastases: time to initiation, switching strategies, and treatment duration. Supportive Care in Cancer, 2019;27(10), pp.3859-3867.

42. Ng T, Tu M, Ibrahim M, Basulaiman BM, McGee S, Srikanthan A et al. Efficacy and toxicity of extending bone modifying agents beyond two years for bone metastases in breast or castrate-resistant prostate cancer patients: A systematic review. Journal of Clinical Oncology. 2020;38:15_suppl, e24083-e24083

Figures (separate PPT and PDF file)

Figure 1 – Consort Diagram
Figure 2 - Subsequent BMA use post systemic disease progression
Figure 3 - Sankey diagram of BMA treatment interval per line of treatment

Tables (as below)

Table 1 - Clinical characteristics comparing patients who did and did not receive BMA
Table 2 - Initial BMA treatment interval
Table 3 - Bone modifying agents: treatment complications

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Table 1: Clinical characteristics comparing patients who did and did not receive BMA

	All patients with bone metastases (n=171)	Patients who received BMA (n=130)	Patients who did not received BMA (n=41)	P value
Mean age in years (range)	58.1 (32 – 87)	58.2 (32-87)	57.9 (33-85)	0.91
Eastern Cooperative Oncology Group performance status				
0-1	160 (94%)	123 (95%)	37 (90%)	0.29
2-4	11 (6%)	7 (5%)	4 (10%)	
Oestrogen Receptor (ER) status				
ER+	118 (69%)	91 (70%)	27 (66%)	0.56
ER-	52 (30%)	38 (29%)	14 (34%)	
Unknown	1 (1%)	1 (1%)	0	
Metastatic sites at time of metastatic breast cancer diagnosis				
Bone only metastases	34 (20%)	31 (24%)	3 (7%)	0.02*
Multiple metastatic sites	137 (80%)	99 (76%)	38 (93%)	
Sites of non-bone metastases				
Visceral	95 (56%)	66 (51%)	29 (71%)	0.03*
Brain/Leptomeningeal	21 (12%)	16 (12%)	5 (12%)	1.00
Nodal	78 (46%)	61 (47%)	17 (41%)	0.59
Other	48 (28%)	35 (27%)	13 (32%)	0.55
First line systemic treatment for metastatic HER2+ breast cancer				
Patients who had 1L chemotherapy				
Docetaxel	49 (29%)	38 (29%)	11 (27%)	0.84
Paclitaxel	75 (43%)	60 (46%)	15 (37%)	0.37
Nab-paclitaxel	12 (7%)	11 (8%)	1 (2%)	0.29
Other	12 (7%)	8 (6%)	4 (10%)	0.48
None	23 (13%)	13 (10%)	10 (24%)	0.032*
Patients who had anti HER2+ treatment				
Trastuzumab	25 (15%)	21 (16%)	4 (10%)	0.45

Trastuzumab and pertuzumab Other None	128 (75%) 4 (2%) 14 (8%)	99 (76%) 3 (2%) 7 (5%)	29 (71%) 1 (2%) 7 (17%)	0.54 1.00 0.043*
Received radiotherapy for bone metastases	46 (27%)	41 (32%)	5 (12%)	0.02*
Location of treatment Metropolitan Regional Victorian Non-Victorian	 157 (92%) 14 (8%) 111 (65%) 60 (35%)	 119 (92%) 11 (8%) 79 (61%) 51 (39%)	 38 (93%) 3 (7%) 32 (78%) 9 (22%)	 1.00 0.06
Overall survival (median)	60.4 months	58.7 months	60.4 months	0.40
Follow up (median)	39.5 months	39.5 months	36.9 months	0.16

Table 2: Initial BMA treatment interval

Initial BMA treatment interval	Overall n=130	Bisphosphonate n=40	Denosumab n=90
4-weekly	55 (42%)	10 (25%)	45 (50%)
6-weekly	49 (38%)	20 (50%)	29 (32%)
12-weekly	14 (11%)	5 (13%)	9 (10%)
Other	4 (3%)	2 (5%)	2 (2%)
Not recorded	8 (6%)	3 (8%)	5 (6%)

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Table 3: Bone modifying agents: treatment complications

Treatment complications	Bisphosphonate n=40	Denosumab n=90
Hypocalcaemia	2 (5%)	7 (8%)
Corrected calcium 1.5-1.74 mmol/L	1 (3%)	2 (2%)
Corrected calcium 1.75-1.9 mmol/L	0	1 (1%)
Corrected calcium 2.0-2.1 mmol/L	1 (3%)	4 (4%)
Osteonecrosis of the jaw	0	3 (3%)

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Figure 1: Consort Diagram