



Research Paper

Adoption of adjuvant bisphosphonates for early breast cancer into standard clinical practice: Challenges and lessons learnt from comparison of the UK and Australian experience



I. Porter^{a,1}, E. Theodoulou^{b,c,1,*}, I. Holen^{b,c}, C. Harper-Wynne^d, S. Baron-Hay^a, C. Wilson^{b,c,1}, J. Brown^{b,c,1}

^a Royal North Shore Hospital, Sydney, Australia

^b Department of Oncology and Metabolism, University of Sheffield, Weston Park Cancer Centre, Sheffield, United Kingdom

^c Sheffield Experimental Cancer Medicine Centre, Sheffield, United Kingdom

^d Kent Oncology Centre, Maidstone Tunbridge Wells NHS Trust, United Kingdom

ARTICLE INFO

Article history:

Received 28 July 2021

Revised 27 October 2021

Accepted 30 October 2021

Available online 1 November 2021

Keywords:

Bisphosphonates

Breast cancer

Adjuvant

Survival

Post-menopausal

ABSTRACT

International guidelines recommend adjuvant bisphosphonates (BPs) for post-menopausal women with early breast cancer to reduce recurrence and mortality. However, globally, wide variation exists in their adoption. In the UK, adjuvant BPs were a recommendation in the breast cancer Clinical Reference Group service specification and were included as a priority for implementation by the national oncologists group UK Breast Cancer Group in November 2015, promoting national uptake, guidance and funding arrangements. In 2018, adjuvant BPs were recommended by the UK's National Institute for Health and Care Excellence. In Australia, adjuvant BPs are still 'off-label' and do not receive national reimbursement or endorsement. To date there has been no research into the prescribing habits of these agents in Australia. With the aim to gather data on adjuvant BPs prescribing practices, online surveys were developed and disseminated to breast oncologists in both countries between December 2018 and June 2019. Almost all of the UK oncologists prescribed adjuvant BPs, demonstrating that education, endorsement from professional bodies, presence of national guidelines and funding decisions have been critical to implementation. In contrast, only 48% of the Australian responders prescribed adjuvant BPs, while 83% reported that they would prescribe them if funding was available. Lack of local protocol guidance was also seen as a major barrier. This study was intended to assess the pathway taken for adjuvant BP implementation in the UK and how it might inform changes in Australian practice and also guide other countries with similar issues with the ultimate aim of improving the care of women with early breast cancer globally.

© 2021 Published by Elsevier GmbH. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Breast cancer (BC) is the most common cancer among women, with 2.1 million cases worldwide each year [1]. Of these, approximately 55,000 new BC cases are diagnosed annually in the UK and 20,000 in Australia. Despite the many advances in anticancer treatments, BC also causes the greatest number of cancer-related deaths among women, with 11,500 and 3,000 annual deaths in the UK and Australia, respectively [2–4].

* Corresponding author at: Department of Oncology and Metabolism, University of Sheffield, Weston Park Cancer Centre, 1st floor Broomcross Building, Whitham Road, Broomhall, Sheffield S10 2SJ, United Kingdom.

E-mail address: e.theodoulou@sheffield.ac.uk (E. Theodoulou).

¹ These authors contributed equally.

In addition to the established use of bisphosphonates (BPs) in patients with bone metastases and to reduce cancer treatment induced bone loss (CTIBL), several early clinical trials of clodronate and zoledronic acid showed a potential benefit in early breast cancer (EBC) in the adjuvant setting, where they were shown to improve survival and reduce bone metastases. These included clodronate trials (Powles et al, [5], Diel et al, [6]) and the ZO-FAST and Z-FAST zoledronic acid studies (Brufsky et al [7], Eidtmann et al [8]). Subsequently, the large AZURE [9] and ABCSG-12 [10] trials demonstrated the benefits of adjuvant zoledronic acid in reducing bone metastasis and improving survival, but only in post-menopausal women (either natural or artificial) and not in pre-menopausal women.

The benefit in post-menopausal patients was confirmed by a meta-analysis published by the Early Breast Cancer Trialists Collaborative Group in 2015 [11], which revealed that among 11,767

post-menopausal women (including pre-menopausal women on ovarian suppression), adjuvant BPs produced highly significant reductions in BC recurrence (HR 0.86, 95% CI 0.78–0.94; $2p = 0.002$), distant recurrence (HR 0.82, 0.74–0.92; $2p = 0.0003$), bone recurrence (HR 0.72, 0.60–0.86; $2p = 0.0002$) and importantly, BC mortality (HR 0.82, 0.73–0.93; $2p = 0.002$). The 10-year risk of death was 14.7% in those treated with adjuvant BPs versus 18.0% in the standard therapy group. This benefit was seen regardless of treatment schedule, oestrogen receptor status, nodal status, tumour grade, or concomitant chemotherapy. There was no difference in outcome between patients receiving nitrogen or non-nitrogen BPs and, with the exception of oral pamidronate, all the other BPs (clodronate, zoledronic acid, ibandronate) produced similar benefit in disease outcomes. Therefore, on average, 33 post-menopausal women need to be treated with adjuvant BPs to prevent 1 BC-related death. Based on these results, the survival benefit of adjuvant BPs in post-menopausal women is comparable to that seen with the addition of taxanes to anthracycline schedules and with the use of aromatase inhibitors versus tamoxifen [12,13].

Denosumab has also been studied in this setting, with somewhat inconsistent results. The ABCSG-18 trial demonstrated reduced fractures [14] and disease-free survival benefit in postmenopausal women with hormone-receptor positive EBC receiving adjuvant aromatase inhibitor (AI) therapy [15]. In contrast, the D-CARE study failed to show improved disease-related outcome from adjuvant use of Denosumab, including in postmenopausal women [16].

Following publication of the 2015 meta-analysis [11], many international guidelines now recommend adjuvant BPs (usually intravenous zoledronic acid every six months for three years or oral clodronate) for post-menopausal women with EBC to reduce recurrence and mortality, particularly for those considered at high risk of BC recurrence [17–21]. Women with high risk of disease recurrence are deemed those who warrant standard adjuvant systemic chemotherapy/HER-2 targeted therapy and/or have greater than 10% 10-year risk of disease relapse. Despite this, wide variation still exists internationally in the adoption of these recommendations. BPs are off-patent with generic formulations being manufactured. Therefore, pharmaceutical lobbying for BPs to gain regulatory approval for this indication is lacking. This may have negative impact on the prescribing of adjuvant BPs, resulting in EBC patients not receiving the intervention. As the majority of EBC patients are (or will become) post-menopausal, it is not just a small subgroup of patients affected by the lack of adjuvant BPs being prescribed.

In the UK, adjuvant BPs were included as a recommendation in the BC Clinical Reference Group service specification and were endorsed as a priority for implementation by the UK Breast Cancer Group (UKBCG) in November 2015, promoting national uptake, guidance and funding arrangements through local commissioning agreements. Two subsequent surveys conducted by UKBCG and the UK charity Breast Cancer Now showed that 24% (March 2016) and 44% (October 2016) of UK oncologists prescribed adjuvant BPs. A repeat survey carried out at the annual UKBCG conference in November 2017 showed that the number of UK oncologists prescribing these agents had increased to 77%. From 2018, adjuvant BPs are also part of the UK's National Institute for Health and Care Excellence (NICE) recommendations for EBC treatment [20]. This is distinct from the use of BPs for prevention of CTIBL and their use in the metastatic setting where they can delay the onset of skeletal related events.

In Australia, several drug therapies are subsidised by the Pharmaceutical Benefits Scheme (PBS) for women with EBC to reduce their chance of BC recurrence and BC related mortality [22]. For women with BC, BPs are available on the PBS for treating osteoporosis, reducing the risk of skeletal related events in patients with BC metastatic to the bone and managing hypercalcaemia of malignancy [22]. However, despite the evidence and recommendation

in international guidelines [17–21], adjuvant BPs are not PBS listed for preventing CTIBL, reducing BC recurrence or improving survival for patients with EBC. On a private script in Australia, the most commonly used BP (zoledronic acid 4 mg) costs between AUD \$50 - \$200 per dose [23]. In addition, Australian states have different funding mechanisms in place. For example, in South Australia, post-menopausal women with a > 10% 10-year recurrence risk can access funded zoledronic acid via their Statewide High Costs Medicines Formulary, whereas no such funding mechanism exists in New South Wales or other Australian states [24].

To date, no surveys have been conducted to document adjuvant BPs prescribing practices of oncologists in Australia. The aim of this international collaboration was to evaluate current practice and indicate barriers to uptake, in order to aid translation of the UK experience of adjuvant BP implementation to Australian practice, potentially paving the way for other nations struggling with similar barriers to ultimately improve outcomes for women with EBC globally.

2. Methods

A collaborative team of Australian and UK oncologists formulated online surveys using a similar template, aiming to evaluate the current use of adjuvant BPs in EBC among UK and Australian Oncologists. The online surveys were developed to cover three broad themes: 1) current practice, 2) patient selection and monitoring, and 3) choice of BP regimen.

In the UK, an anonymous, online, 15-item self-administered survey was designed by using SurveyMonkey, an online survey development software. The survey link was distributed via email through the UKBCG to 277 Medical and Clinical Oncologists treating BC patients across a number of UK centres. The initial invitation was sent in March 2019, followed by a reminder email in May 2019. The survey remained open between March 2019 and June 2019, no incentive to participate was provided.

In Australia, an anonymous, electronic, 17-item self-administered survey was distributed via email and social media to medical oncologists and medical oncology advanced trainees. Email distribution was facilitated via the Breast Cancer Trials Group (256 recipients), work place e-mails (38 recipients) and advanced trainee social media page (150 recipients) between December 2018 and April 2019. No incentive was provided. The total number of participants reached via these avenues was 444, although we anticipate there would have been considerable overlap in recipients. The survey was not limited to one distribution list so as to allow more responses and try and achieve input from a broad mix of medical oncologists and medical oncology trainees. Medical oncology advanced trainees were included as insight into the prescribing habits of their consultants and of those soon to be entering the work force as new consultants.

Descriptive statistics were used to summarise the responses to the survey. The data was compiled using Microsoft Office Excel (© 2018 Microsoft Corporation). Percentages were rounded to nil decimal point.

The results of the UK and Australian surveys and the UK experience were used in a collaborative manner to understand the health economics and promote the deliverability of adjuvant BPs to women with EBC in Australia.

3. Results

3.1. Current practice

3.1.1. Role of clinicians

The UK survey received 68 responses (25% response rate). Ninety-six percent of the participants were consultant oncologists

(50% medical oncologists, 46% clinical oncologists) and 4% were at a non-consultant level. Replies were received from all four UK countries, with the vast majority of responders (99%) working as NHS oncologists.

The Australian survey received 60 responses (14% response rate, not accounting for overlap). Of the 60 participants, 22 (37%) were consultant medical oncologists working in both the public and private sectors, 20 (33%) were consultant medical oncologists working in the public sector only, 11 (18%) were medical oncology advanced trainees and 7 (12%) were consultant medical oncologists working in the private sector only. Overall, the participants were experienced in treating EBC, with 33% treating >80 patients with a new diagnosis of EBC each year, 25% treating between 51 and 80, 33% treating between 21 and 50 and only 8% treating less than 20 new patients with EBC each year. Although geographic data was not specifically captured, there was evidence of participation from multiple Australian states noted in the comments of respondents.

3.1.2. Awareness of guidelines

Participants were asked about the awareness of the following guidelines for the use of adjuvant BPs: UK Breast Cancer Group (UKBCG) 2015, European Society of Medical Oncology (ESMO) 2016, American Society of Clinical Oncology and Cancer Care Ontario (ASCO/CCO) 2017, National Comprehensive Cancer Network (NCCN) and National Institute for Health and Care Excellence (NICE) 2018. Most (85%) of the UK oncologists were following the UKBCG guidelines regarding the prescription of adjuvant BPs to prevent disease recurrence in women with EBC, with 26% following NICE guidelines (Fig. 1). UK oncologists were also familiar with the ASCO/CCO recommendations and ESMO guidelines, but only 9% and 5% respectively stated that they were following them.

The majority of Australian participants (83%) were familiar with the joint ASCO/CCO guidelines. Other guidelines with familiarity included NCCN (39%) and ESMO (32%) (Fig. 1). Only one participant reported not being familiar with any guidelines on the topic.

3.1.3. Prescribing habits

At the point of the UKBCG survey (June 2019), almost all of the UK oncologists (99%) were prescribing adjuvant BPs to patients with EBC for the prevention of disease recurrence, showing a 75% increase since the first survey in March 2016 (Fig. 2). An analysis of the UK national Systemic Anticancer Treatment (SACT) dataset for the prescribing of adjuvant zoledronic acid, showed a clear increase in use over the period from 2017 to 2020 (Fig. 3).

In contrast, although 50 of the 60 Australian responders (83%) reported that they would prescribe a bone modifying agent (BMA) if it was listed on the PBS for the adjuvant management of EBC to prevent disease recurrence, only 48% were actually prescribing them for this purpose.

3.1.4. Barriers to prescribing

As illustrated in Fig. 2, adjuvant BP prescription has increased rapidly and is now almost universal amongst UK clinicians. The reasons given by the single UK oncologist who was not offering adjuvant BPs in EBC were the local protocol guidance and the difficulties in accessing an infusion chair (required for administration of zoledronic acid).

For the Australian clinicians, of the 21 participants who did not currently prescribe adjuvant BPs, 16 (76%) reported that it was due to cost concerns, whereas 8 (38%) were not convinced by the available data regarding significant patient benefit (Fig. 4). For the entire population surveyed, major barriers to prescribing BPs in Australia were identified as being cost (80%), local protocol guidance (36%) and lack of awareness of the current data (31%). Side effects (29%) and patient reluctance to additional treatment (22%) were also considered barriers. Only 3 responders (5%) stated that

they would not prescribe BMAs for the adjuvant management of EBC, even if they were part of the Australian PBS, with an additional 7 (12%) stating that they were unsure.

3.2. Patient selection and monitoring

3.2.1. Patient identification and characteristics

The majority (68%) of the UK respondents reported that the use of adjuvant BPs to prevent disease recurrence was discussed in their BC multidisciplinary team (MDT) meetings. In contrast, the topic was only addressed in 18% of responding Australian oncologists' MDTs. Despite MDT meetings being run in similar ways in the UK and Australia, the discussion about adjuvant BPs differs markedly between the two countries, highlighting the need for funding, protocol guidance and increased awareness of patient benefit in the Australian practice.

Post-menopausal women at high risk of disease recurrence were the main group of BC patients who received adjuvant BMAs in both the UK (97%) and Australia (79%) (Fig. 5). For 85% of the UK participants, those at high risk of disease recurrence included post-menopausal women who would be offered chemotherapy (irrespective if they received it or not). Other reasons for considering a post-menopausal BC patient at high risk of recurrence were node positive (3%) and large node positive disease (2%), and > 2% (2%) and > 10% (2%) benefit on PREDICT scoring. A high risk of recurrence is a major determinant for prescribing, as only 3% and 17% of the UK and Australian oncologists, respectively, were prescribing adjuvant BMAs to all post-menopausal women regardless of their risk of disease recurrence.

Pre-menopausal women receiving GnRH (gonadotrophin releasing hormone) analogues were prescribed adjuvant BMAs by 68% of UK clinicians and 31% of Australian clinicians (Fig. 5).

3.2.2. Bone mineral density and dental assessments

Due to the risk of CTIBL, bone mineral density (BMD) assessments are considered in women with EBC who receive systemic anticancer therapy and endocrine treatment such as aromatase inhibitors (AIs) and also in those women rendered prematurely menopausal by their adjuvant chemotherapy. Use of adjuvant BPs in this group of women can have a dual effect by reducing both the risk of recurrence and the risk of CTIBL. Dental assessments are recommended prior to commencing adjuvant BPs in all patients in order to reduce the risk of BP-related osteonecrosis of the jaw. 92% of the UK oncologists mandated dental assessment for all the EBC patients who would receive adjuvant BPs.

In the cases where adjuvant BPs were given, 82% of the UK oncologists did not routinely perform BMD assessments prior to commencing BPs (Fig. 6). However, 35% did perform these at the completion of duration of BPs (after up to 3 years), in order to be used as baseline scans for future reference. If the patients were on extended endocrine treatment after the completion of adjuvant BPs, 39% of the UK oncologists performed BMD assessments every 2 years, while 36% did not measure BMD in this group of patients.

In the Australian survey, 93% ordered a BMD assessment prior to starting an aromatase inhibitor for women with EBC. However, 28% reported that this would not be required if commencing an adjuvant BMA (Fig. 6). There was a wide spectrum of practice when it came to the frequency of ordering BMDs with the majority between 1 and 3 years and many taking into consideration the baseline result.

3.3. Choice of bone modifying agent (BMA) regimen

3.3.1. Commonly prescribed regimen

The meta-analysis demonstrated that all the BPs, apart from the oral pamidronate, showed similar benefits in terms of disease out-

Which guidelines are you aware of?

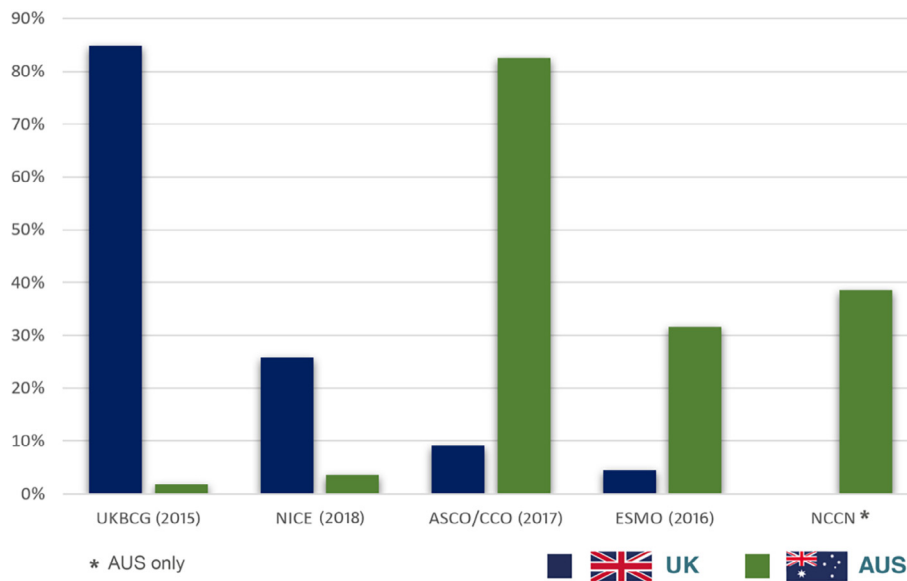


Fig. 1. Awareness of BMAs published guidelines amongst UK and Australian clinicians (multiple choice question).

Use of Adjuvant BMAs in the UK and AUS

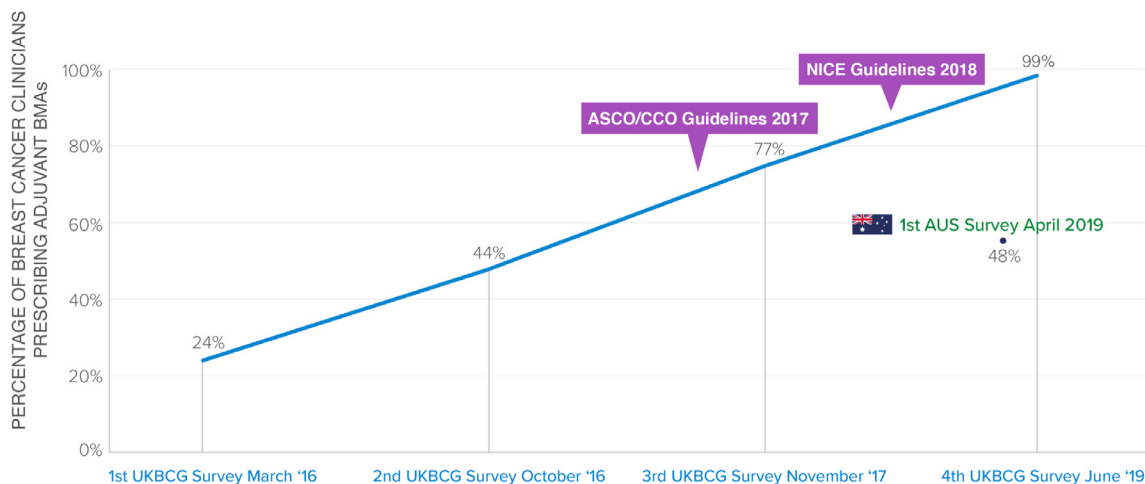


Fig. 2. Historical data for the use of adjuvant BMAs in EBC in the UK and Australia.

comes for postmenopausal patients with early BC. In terms of duration and intensity of treatment, there was no difference between less than 2 years or 3–5 years of treatment and between monthly and 6 monthly regimes [6].

Intravenous zoledronic acid (4 mg/6-monthly) was the most commonly prescribed adjuvant BMAs in both countries (89% UK, 81% Australia) and most responders offered BMAs for prevention of disease recurrence for a duration of 3 years. Zoledronic acid for the period that patient was receiving systemic anticancer treatment followed by oral ibandronic acid when chemotherapy finished, was the second most common regimen in the UK (27%), while 6-monthly denosumab was prescribed by 36% of the Australian oncologists with the intention of preventing disease recurrence. The results of the large D-CARE study [9], reported in December 2019, showed no benefit of adjuvant denosumab in EBC and therefore this will likely have had an impact on the Australian practice since the time of our survey.

3.3.2. Supportive medications

The guidelines state that vitamin D and calcium supplements should be offered to patients who are on adjuvant BPs.

In the UK survey, 89% of the responders prescribed both vitamin D and calcium alongside BMAs in order to prevent hypocalcemia and undiagnosed vitamin D deficiency.

In the Australian survey, 98% of participants prescribed vitamin D and 83% prescribed calcium alongside BMAs. Only 3% reported that they prescribed exercise alongside BMAs; there was no question about prescribed exercise in the UK survey.

4. Discussion

As a result of published international data, the sub-analysis of the AZURE trial and the subsequent confirmed results of the large 2015 meta-analysis [5–11], adjuvant BPs have now become standard of care to reduce BC mortality in post-menopausal EBC

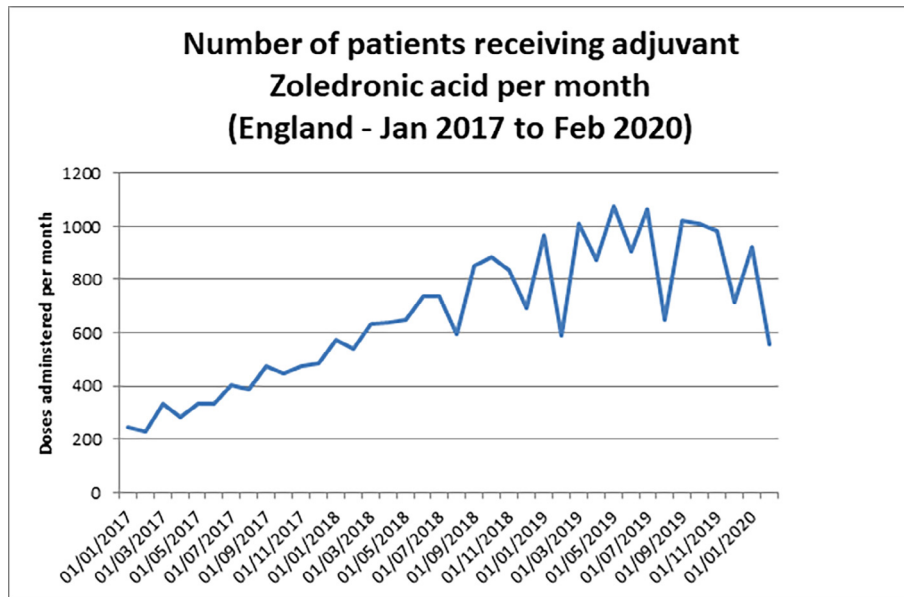


Fig. 3. Hospital usage by doses of the zoledronic acid used in adjuvant BC in England (2017–2020).

What do you see as the major barriers to prescribing BMAs for prevention of disease recurrence?

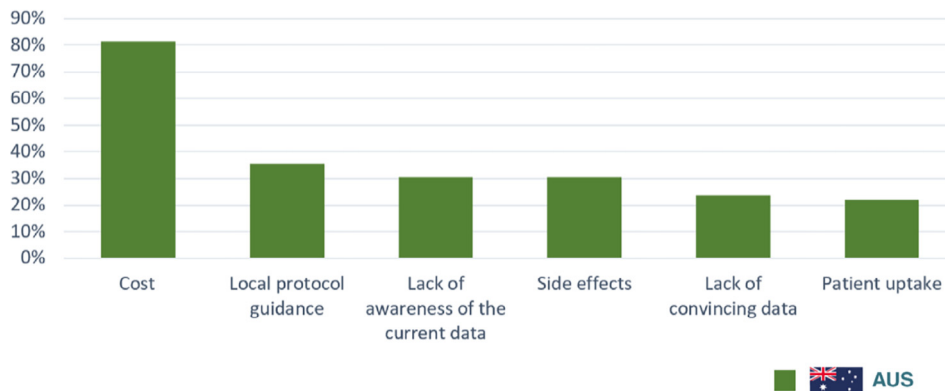


Fig. 4. Barriers to BMAs prescribing for Australian clinicians (multiple choice question).

patients in the UK as well as the rest of Europe and America, supported by published guidelines on drug choice, duration and patient selection [17–21]. Interestingly, a very recent study reported that extending adjuvant zoledronic acid treatment beyond 2 years did not improve the prognosis of high-risk patients with EBC receiving chemotherapy and that current recommendations for 3 – 5 years of treatment could be relaxed [25].

In addition, a recent survey of Canadian EBC patients treated or undergoing adjuvant BP therapy (92% zoledronic acid) demonstrates the therapy is tolerable with a 94% completion rate, despite 60% of patients experiencing one or more side effects [26]. However, uptake in other countries, including Australia, has been slower, suggesting that a large number of patients are missing out on potentially life-saving adjuvant therapy. It is therefore important to explore the barriers to wider uptake, in order to improve patient benefit more widely.

The Australian survey results are representative of a group of practicing Australian medical oncologists and trainees in both public and private settings, with significant experience in treating women with EBC (58% seeing >50 new EBC patients per year) and knowledge of current guidelines on the topic. The vast majority (83%) of those surveyed supported the use of adjuvant BPs in post-menopausal women with EBC for prevention of disease recurrence, especially in those considered high risk. Despite this, uptake in Australia remains heterogenous and sub-optimal, with less than 50% of respondents currently prescribing adjuvant BPs, compared with almost all of the oncologists in the UK. Similar to the historical UK experience, the main barriers identified in Australia were lack of national funding, local protocol guidance and physician awareness.

Despite the lack of clear guidelines to support the use of adjuvant denosumab to improve overall survival, 18% of Australian

How do you select women with EBC for adjuvant BMAs for prevention of disease recurrence?

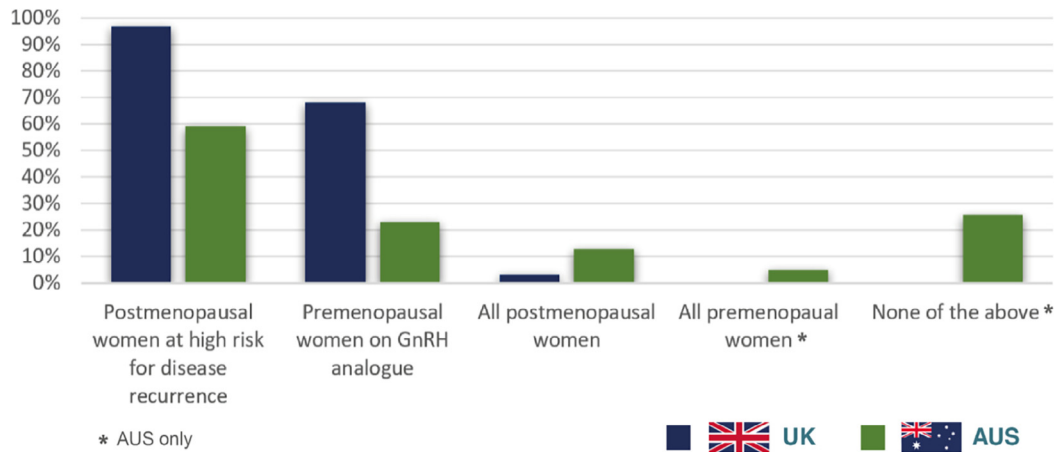


Fig. 5. Patient selection for adjuvant BMAs in the UK and Australia (multiple choice question).

Do you routinely perform bone density assessment prior to starting adjuvant BMA for prevention of disease recurrence?

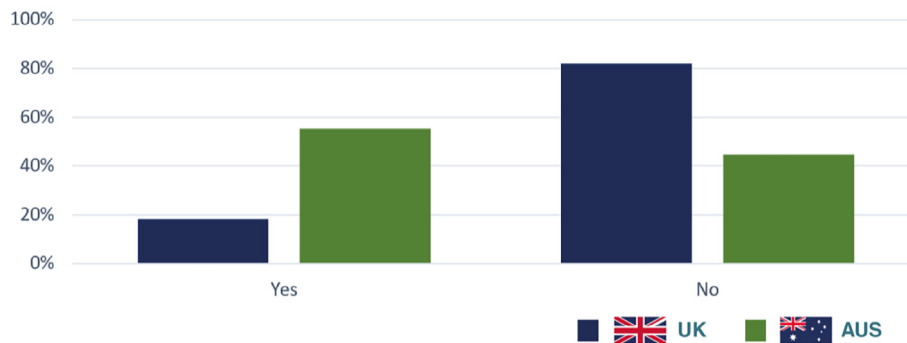


Fig. 6. BMD assessments prior to initiation of BMAs for prevention of disease recurrence.

clinicians surveyed were prescribing it, compared with none of the surveyed UK clinicians. The rationale for such significant use of denosumab in the adjuvant setting in Australia was not documented by this study, but may at least in part be due to outcome benefits in terms of greatly reduced fracture rate [14] and improved disease-free survival [15] from 6 monthly use of denosumab in addition to adjuvant AI therapy reported in the ABCSG-18 trial. In addition, there may have been a lack of awareness of the D-CARE trial data as the final results were published after the completion of this survey [16]. Finally, there may have been extrapolation from the use of denosumab in CTIBL, where it has performed as well as/better than BPs [14] and been more convenient for patients and does not require chair time in busy outpatient chemotherapy treatment facilities. In addition to their survival benefit, BPs also prevent CTIBL. In the cases where BPs are given for prevention of disease recurrence, a considerable percentage of Australian oncologists were experiencing the same barriers in routinely performed BMD assessment prior to commencing BMAs, demonstrating a potential avenue for cost saving.

Considering the absolute overall survival benefit of adjuvant BPs the addition of zoledronic acid to the entire eligible Australian population (~15,000) [3,4,27] has the potential to reduce annual BC deaths by ~ 400. BC experts have already been working with the Medical Oncology Group of Australia (MOGA) and various sponsors to fund adjuvant BP therapy. However, pharmaceutical companies do not see a return on these drugs now they are off-patent, and there is a reluctance for them to bring forward applications for these indications. Therefore, rather than just focus on the humanitarian aspects, an Australian-specific business case is required to move this issue forward. This business case could be modelled on those done in the UK that demonstrate substantial cost benefit of £456 k per annual cohort of patients in Scotland and £4.22 m per annual cohort in England [28]. Until a business case and financial impact statement can be developed to increase the likelihood of obtaining national funding, we recommend that development of national guidelines endorsing BP use in the adjuvant setting should be prioritised, as well as improving awareness of the data amongst clinicians and patients.

Table 1
Proposed steps to increase update of adjuvant BPs in EBC.

Proposed steps to increase update of adjuvant BPs in Early Breast Cancer
Raise awareness of the adjuvant BPs benefits by engaging with the oncology community (oncology conferences etc)
Encourage the discussion of adjuvant BPs in local breast cancer MDT meetings
Work with national bodies to produce clear guidelines for the use of adjuvant BPs in EBC
Develop a convincing business case to demonstrate value for money
Work with breast cancer charities (local, regional and national) to raise awareness among patients and lobby decision makers

In the UK, the leading BC charity Breast Cancer Now was heavily engaged in raising awareness of the benefits of adjuvant BPs amongst patients lobbying the Department of Health and Social Care and NHS England to clarify commissioning responsibility and advice, helping hospital trusts to make the case for their use, and worked to generate significant media coverage on this issue. Currently the prescription of adjuvant BPs is not mentioned on prominent Australian BC sites such as Breast Cancer Network Australia [29] and the National Breast Cancer Foundation [30]. In September 2020, Cancer Australia updated its 2001 guidelines for the management of EBC which do now address this important topic with the latest evidence and recommend oncologists 'consider' adjuvant BPs for postmenopausal women at moderate to high risk of recurrence and premenopausal women receiving ovarian suppression, though noting that zoledronic acid is not approved by the Therapeutic Goods Association for the indication [31]. It should also be noted that, although not available at the time of the survey, new ESMO guidelines were published in 2020, stating that 'the addition of a bisphosphonate to standard adjuvant therapies for postmenopausal early breast cancer reduces bone recurrence and improves survival' [32].

There are several limitations to this cross-sectional study. This study includes representative data from participants from each survey, but both had a relatively low response rate which may limit its generalisability to practice as a whole requiring caution in interpretation although, in the Australian survey, as outlined in the Methods Section, we anticipate there would have been considerable overlap between the various platforms used to distribute the Australian survey to recipients. Response bias from distribution via specialist BC membership lists could potentially over-estimate the current prescription of adjuvant BPs given the high rates of BC specialisation, penchant for research and international collaboration within the group. However, the data in Fig. 3 clearly shows the increase in monthly doses of adjuvant zoledronic acid administered in England between January 2017 and January 2020. These data support the conclusion that prescribing has changed dramatically over the years, presumably due to the national education campaign run through Sheffield and NICE and UKBCG endorsement.

A similar Canadian clinicians' survey published in 2019 also had a low response rate at 11% (68/618), suggesting that this is not uncommon for this type of survey-based study [33]. However, a further Canadian physician survey exploring the same topic and also asking participants to suggest future research ideas on adjuvant BPs, had 41% response rate (52/127) [34]. This higher response rate may be due to the more targeted group of participants.

With regards to the Australian data, additional information on participants affiliated institutions may have been helpful in determining variances in practice between states, given the different funding arrangements that exist. The Australian exercise also did not gather data on the clinical factors and predictive tools clinicians use to categorise a patient 'high-risk' for recurrence, whereas the UK data gave some insight to this. Better targeted patient selection may become more apparent as new literature on predictive biomarkers (such as MAF status as identified in the updated AZURE analysis) becomes available [35]. It should be recognised that this survey was carried out before the COVID-19 pandemic, where, in the UK, there is evidence of a switch from IV BP use to oral BP use

in order to reduce the need for hospital attendance [36]. Whether this pattern will revert post-pandemic or whether there will be a permanent shift towards oral adjuvant BPs remains to be seen.

Despite these limitations, this study reports relevant data demonstrating that the vast majority of Australian participants support the prescription of adjuvant BPs to post-menopausal women with EBC, but are currently unable to incorporate this into their practice. In addition, the data support that in the UK, use of adjuvant BPs has continued to increase, with responders stating clear guidelines from national bodies such as NICE and UKBCG and funding arrangements have been crucial for the high UK uptake. Like the UK experience, we hope the data we present will aid in the formulation of a business case, lobbying for reimbursement and developing national consensus guidelines in Australia (Table 1). If we are able to address the major barriers of cost, physician awareness and local protocol guidance, this would lead to more optimal management of Australian women with EBC and allow their oncologists to conform to international practice.

Currently, data on adoption rates from other countries do not appear to be available, with the exception of the 2021 clinician survey from Canada in which most responders (77.4%) recommending adjuvant BMAs (mainly zoledronic acid 4 mg/6monthly) for post-menopausal patients with high-risk breast cancer [34]. However, this high rate amongst the survey responders was not reflected by prescription data; e.g in Ontario only 20% of eligible patients received adjuvant BPs. The authors highlight that this may be due to selection bias in terms of survey responders, which may also be an element in our data, resulting in higher uptake rate than in the general oncology community. Interestingly, in this study the main barriers to wider uptake were identified as increased risk of toxicities from BMAs and the need for additional follow up and treatment.

We believe that further collaborations with countries where adjuvant BPs are not part of their standard of care in EBC, would help their regulatory bodies to adopt this life saving treatment. Furthermore, we hope that by translating the methodology for adjuvant BP implementation in the UK to Australia, that this may also pave the way for other nations struggling with similar barriers to ultimately improve outcomes for women with EBC globally.

CRediT authorship contribution statement

I. Porter: Methodology, Investigation, Formal analysis, Writing – original draft, Visualization. **E. Theodoulou:** Investigation, Methodology, Formal analysis, Visualization, Writing – original draft. **I. Holen:** Supervision, Writing – review & editing. **C. Harper-Wynne:** Methodology, Conceptualization, Writing – review & editing. **S. Baron-Hay:** Methodology, Conceptualization, Writing – review & editing. **C. Wilson:** Methodology, Conceptualization, Writing – review & editing, Supervision. **J. Brown:** Methodology, Conceptualization, Writing – review & editing, Supervision.

Declaration of Competing Interest

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

Acknowledgements

We wish to thank all the respondents to both the UK and Australian surveys, to Breast Cancer Network Australia for helping to distribute the Australian survey and UKBCG for helping distribute the UK survey. We are also grateful to Neil Masters, Principal Pharmacist SACT Transformation Programme, Weston Park Cancer Centre, Sheffield, UK, for providing the analysis for Fig. 3. We also thank Yorkshire Cancer Research for the award of a fellowship to ET.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jbo.2021.100402>.

References

- [1] World Health Organisation, Breast cancer. <https://www.who.int/cancer/prevention/diagnosis-screening/breast-cancer/en>, 2019 (accessed 23 May 2019)
- [2] Breast Cancer Now, Facts and statistics 2021. <https://breastcancernow.org/about-us/media/facts-statistics>, 2021 (accessed 25 March 2021).
- [3] Australian Institute of Health and Welfare & Cancer Australia 2012. Breast cancer in Australia: an overview. Cancer series no. 71. Cat. no. CAN 67. Canberra: AIHW.
- [4] Cancer Australia, Breast cancer statistics. <https://breast-cancer.canceraustralia.gov.au/statistics>, 2019 (accessed 29 July 2019).
- [5] T. Powles, A. Paterson, E. McCloskey, P. Schein, B. Scheffler, A. Tidy, S. Ashley, I. Smith, L. Ottestad, J. Kanis, Correction: Reduction in bone relapse and improved survival with oral clodronate for adjuvant treatment of operable breast cancer [ISRCTN83688026], *Breast Cancer Res.* 8 (3) (2006) 406, <https://doi.org/10.1186/bcr1413>.
- [6] I.J. Diel, A. Jaschke, E.F. Solomayer, C. Gollan, G. Bastert, C. Sohn, F. Schuetz, Adjuvant oral clodronate improves the overall survival of primary breast cancer patients with micrometastases to the bone marrow—a long-term follow-up, *Ann Oncol.* 19 (12) (2008) 2007–2011, <https://doi.org/10.1093/annonc/mdn429>.
- [7] A. Brufsky N. Bundred R. Coleman R. Lambert-Falls R. Mena P. Hadji L. Jin N. Schen S. Ericson E.A. Perez 13 5 2008 503 514
- [8] H. Eidtmann, R. de Boer, N. Bundred, A. Llombart-Cussac, N. Davidson, P. Neven, G. von Minckwitz, J. Miller, N. Schenk, R. Coleman, Efficacy of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36-month results of the ZO-FAST Study, *Ann Oncol.* 21 (11) (2010) 2188–2194, <https://doi.org/10.1093/annonc/mdq217>.
- [9] R.E. Coleman, M. Collinson, W. Gregory, H. Marshall, R. Bell, D. Dodwell, M. Keane, M. Gil, P. Barrett-Lee, D. Ritchie, A. Bowman, V. Liversedge, R.H. De Boer, J.L. Passos-Coelho, S. O'Reilly, G. Bertelli, J. Joffe, J.E. Brown, C. Wilson, J.C. Terceiro, J. Jean-Mairet, R. Gomis, D. Cameron, Benefits and risks of adjuvant treatment with zoledronic acid in stage II/III breast cancer: 10 years follow-up of the AZURE randomized clinical trial (BIG 01/04), *J Bone Oncol.* 13 (2018) 123–135, <https://doi.org/10.1016/j.jbo.2018.09.008>.
- [10] M. Gnant, B. Mlineritsch, W. Schippering, G. Luschin-Ebengreuth, S. Pöstlberger, C. Menzel, R. Jakesz, M. Seifert, M. Hubalek, V. Bjelic-Radisic, H. Samonigg, C. Tausch, H. Eidtmann, G. Steger, W. Kwasny, P. Dubsy, M. Fridrik, F. Fitzal, M. Stierer, E. Rücklinger, R. Greil, ABCSG-12 Trial Investigators, C. Marth, Endocrine therapy plus zoledronic acid in premenopausal breast cancer, *N Engl J Med.* 360 (7) (2009) 679–691, <https://doi.org/10.1056/nejmoa0806285>.
- [11] Early Breast Cancer Trialists' Collaborative Group, Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials, *Lancet.* 386 (10001) (2015) 1353–1361, [https://doi.org/10.1016/S0140-6736\(15\)60908-4](https://doi.org/10.1016/S0140-6736(15)60908-4).
- [12] A. Eisen M. Trudeau W. Shelley H. Messersmith K.I. Pritchard Aromatase inhibitors in adjuvant therapy for hormone receptor positive breast cancer: A systematic review *Cancer Treat Rev.* 34 2 10.1016/j.ctrv.2007.11.001. 2008, pp. 157–74 <https://doi.org/>
- [13] J.A. Sparano, M. Wang, S. Martino, V. Jones, E.A. Perez, T. Saphner, A.C. Wolff, G. W. Sledge, W.C. Wood, N.E. Davidson, Weekly Paclitaxel in the Adjuvant Treatment of Breast Cancer, *N Engl J Med.* 358 (16) (2008) 1663–1671, <https://doi.org/10.1056/NEJMoa0707056>.
- [14] M. Gnant, G. Pfeiler, P.C. Dubsy, M. Hubalek, R. Greil, R. Jakesz, V. Wette, M. Balic, F. Haslbauer, E. Melbinger, V. Bjelic-Radisic, S. Artner-Matuschek, F. Fitzal, C. Marth, P. Sevela, B. Mlineritsch, G.G. Steger, D. Manfreda, R. Exner, D. Egle, J. Bergh, F. Kainberger, S. Talbot, D. Warner, C. Fesl, C.F. Singer, Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial, *Lancet.* 386 (9992) (2015) 433–443, [https://doi.org/10.1016/S0140-6736\(15\)60995-3](https://doi.org/10.1016/S0140-6736(15)60995-3).
- [15] M. Gnant, G. Pfeiler, G.G. Steger, D. Egle, R. Greil, F. Fitzal, V. Wette, M. Balic, F. Haslbauer, E. Melbinger-Zeinitzer, V. Bjelic-Radisic, R. Jakesz, C. Marth, P. Sevela, B. Mlineritsch, R. Exner, C. Fesl, S. Frantal, C.F. Singer, Austrian Breast and Colorectal Cancer Study Group, Adjuvant denosumab in postmenopausal patients with hormone receptor-positive breast cancer (ABCSG-18): disease-free survival results from a randomised, double-blind, placebo-controlled, phase 3 trial, *Lancet Oncol.* 20 (3) (2019) 339–351, [https://doi.org/10.1016/S1470-2045\(18\)30862-3](https://doi.org/10.1016/S1470-2045(18)30862-3).
- [16] R. Coleman D.M. Finkelstein C. Barrios M. Martin H. Iwata R. Hegg J. Glaspy A. M. Periañez K. Tonkin I. Deleu J. Sohn J. Crown S. Delaloge T. Dai Y. Zhou D. Jandial A. Chan 21 1 2020 60 72
- [17] S. Dhesy-Thind, G.G. Fletcher, P.S. Blanchette, M.J. Clemons, M.S. Dillmon, E.S. Frank, S. Gandhi, R. Gupta, M. Mates, B. Moy, T. Vandenberg, C.H. Van Poznak, Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline, *J Clin Oncol.* 35 (18) (2017) 2062–2081, <https://doi.org/10.1200/JCO.2016.70.7257>.
- [18] P. Hadji, R.E. Coleman, C. Wilson, T.J. Powles, P. Clézardin, M. Aapro, L. Costa, J.J. Body, C. Markopoulos, D. Santini, I. Diel, A. Di Leo, D. Cameron, D. Dodwell, I. Smith, M. Gnant, R. Gray, N. Harbeck, B. Thurlimann, M. Untch, J. Cortes, M. Martin, U.S. Albert, P.F. Conte, B. Ejlersen, J. Bergh, M. Kaufmann, I. Holen, Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel, *Ann Oncol.* 27 (3) (2016) 379–390, <https://doi.org/10.1093/annonc/mdv617>.
- [19] M. Gnant N. Harbeck C. Thomssen St. Gallen, Vienna, A Brief Summary of the Consensus Discussion about Escalation and De-Escalation of Primary Breast Cancer Treatment *Breast Care.* 12 2 2017 2017, pp. 102–7 10.1159/000475698
- [20] National Institute for Health and Care Excellence (NICE), Early breast cancer (preventing recurrence and improving survival): adjuvant bisphosphonates. <https://www.nice.org.uk/advice/es15/chapter>, 2017 (accessed 19 June 2019)
- [21] A. Bharatuar, M. Kar, S. Khatir, V. Goswami, R. Sarin, S. Dawood, R. Iyenger, M. Ganvir, P.M. Parikh, S. Aggarwal, V. Talwar, Practical consensus recommendation for adjuvant bone-modifying agents in breast cancer, *South Asian J Cancer.* 7 (2) (2018) 91–95, https://doi.org/10.4103/sajc.sajc_109_18.
- [22] Australian Government Department of Health, Pharmaceutical Benefits Scheme (PBS). <http://www.pbs.gov.au/pbs/home>, 2019 (accessed 2 October 2019).
- [23] MIMS online, Zoledronic acid. <https://www.mimsonline.com.au.acs.hcn.com.au>, 2018 (accessed 13 October 2019).
- [24] SA Health, High cost medicine reviews. <https://www.sahealth.sa.gov.au>, 2019 (accessed 7 October 2019).
- [25] T.W.P. Friedl, T. Fehm, V. Müller, W. Lichtenegger, J. Blohmer, R. Lorenz, H. Forstbauer, V. Fink, I. Bekes, J. Huober, J. Jückstock, A. Schneeweiss, H. Tesch, S. Mahner, S.Y. Brucker, G. Heinrich, L. Häberle, P.A. Fasching, M.W. Beckmann, R. E. Coleman, W. Janni, B. Rack, Prognosis of Patients With Early Breast Cancer Receiving 5 Years vs 2 Years of Adjuvant Bisphosphonate Treatment: A Phase 3 Randomized Clinical Trial, *JAMA Oncol.* 7 (8) (2021) 1149–1157, <https://doi.org/10.1001/jamaoncol.2021.1854>.
- [26] S. McGee, M. Alzahrani, C. Stober, T.L. Ng, K.M. Cole, G. Larocque, A.A. Awan, S. Sehdev, J.F. Hilton, L. Vandermeer, B. Hutton, G.R. Pond, D. Saunders, M. Clemons, Adjuvant bisphosphonate use in patients with early stage breast cancer: Patient perspectives on treatment acceptability and potential de-escalation, *J Bone Oncol.* 27 (2021), <https://doi.org/10.1016/j.jbo.2021.100351>.
- [27] S.J. Lord, M.L. Marinovich, J.A. Patterson, N. Wilcken, B.E. Kiely, V. GebSKI, S. Crossing, D.M. Roder, M. Gattellari, N. Houssami, Incidence of metastatic breast cancer in an Australian population-based cohort of women with non-metastatic breast cancer at diagnosis, *Med J Aust.* 196 (11) (2012) 688–692, <https://doi.org/10.5694/mja12.10026>.
- [28] Breast cancer now, Summary of adjuvant bisphosphonates Scotland. https://breastcancernow.org/sites/default/files/160825_breast_cancer_now_-_summary_of_adjuvant_bisphosphonates_-_scotland_0.pdf, 2019 (accessed 15 June 2019).
- [29] Breast Cancer Network Australia, Breast cancer treatments. <https://www.bcna.org.au/understanding-breast-cancer/treatment/>, 2021 (accessed 25 March 2021).
- [30] National Breast Cancer Foundation, Breast cancer treatment. <https://nbcf.org.au/about-breast-cancer/treatment/>, 2021 (accessed 25 March 2021).
- [31] Cancer Australia, Guidance for the management of early breast cancer. <https://www.guidancebreastcancer.gov.au/treatment-systemic-therapy/bone-modifying-agents-and-bone-health/adjuvant-bisphosphonate-treatment-premenopausal-women>, 2020 (accessed 25 March 2021).
- [32] R. Coleman, P. Hadji, J.J. Body, D. Santini, E. Chow, E. Terpos, S. Oudard, Ø. Bruland, P. Flamen, A. Kurth, C. Van Poznak, M. Aapro, K. Jordan, on behalf of the ESMO Guidelines Committee, Bone health in cancer: ESMO Clinical Practice Guidelines, *Ann Oncol.* 31 (2020) 165–1663, <https://doi.org/10.1016/j.annonc.2020.07.019>.
- [33] L. Zibdawi D. Simos S. Kassam A. Rana F. Kassam Y. Rahim Clinical practice patterns on the use of adjuvant bisphosphonate for early breast cancer: A Canadian perspective *J Clin Oncol.* 37 2019 12002 12002 10.1200/JCO.2019.37.15_suppl.e12002
- [34] S. McGee, M. Alzahrani, L. Vandermeer, K. Cole, G. Larocque, A. Awan, B. Hutton, G. Pond, D. Saunders, M. Clemons, Adjuvant bisphosphonate use in patients with early breast cancer: a physician survey, *Breast Cancer Res Treat.* 187 (2021) 477–486, <https://doi.org/10.1007/s10549-021-06147-1>.
- [35] A.H. Paterson S.J. Anderson R. Gomis J. Jean-Mairet@inbiomotion.com, J.C. Terceco, P. Lucas, E.P. Mamounas, Validation of MAF biomarker for response

prediction to adjuvant bisphosphonates in 2 clinical trials: AZURE and NSABP-B34 J Clin Oncol. 38 2020 513 513 10.1200/JCO.2020.38.15_suppl.513
[36] J.E. Brown, S.L. Wood, C. Confavreux, M. Abe, K. Weilbaeher, P. Hadji, R.W. Johnson, J.A. Rhoades, C.M. Edwards, P.I. Croucher, P. Juarez, S. El Badri, G.

Ariaspinilla, S. D'Oronzo, T.A. Guise, C. Van Poznak, Management of bone metastasis and cancer treatment-induced bone loss during the COVID-19 pandemic: An international perspective and recommendations, J Bone Oncol. 29 (2021), <https://doi.org/10.1016/j.jbo.2021.100375> 100375.