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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

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ABSTRACT

Background: There remain questions around the optimal use of bone-modifying agents (BMAs) in patients with bone metastases from breast and castration-resistant prostate cancer (CRPC). A physician survey was performed to identify current practices, as well as perceptions around long-term BMA use, BMA de-escalation, and further BMA de-escalation after 2 years of use.

Methods: Canadian oncologists treating breast cancer or CRPC were surveyed via an anonymized online survey. The survey collected physician demographics, current practice patterns, perception on risk of symptomatic skeletal events (SSE) and BMA-associated toxicities, and attitudes towards further de-escalation of BMAs after 2 years of treatment.

Results: A total of 334 physicians in Canada were contacted, of which 295 were eligible on initial screening, and 65 completed the survey (response rate 22%): 35 treated breast cancer, 25 treated prostate cancer and 5 treated both. The most common BMA regimens in patients with no limitation in drug coverage were denosumab q4wks for 3–4 months followed by a de-escalation to q12wks (breast cancer) and denosumab q4wks (prostate cancer). In patients with provincial health coverage only the common choices were zoledronate q4wks for 3–4 months followed by de-escalation to q12wks (breast cancer) and denosumab q4wks (prostate cancer). There was equipoise regarding the benefit of continuing BMA beyond 2 years and interest in further trials of de-escalation of BMA in both breast and prostate cancer. The most favored alternative primary study endpoints to SSE were BMA toxicity (67.2%), pain (46.9%), and physical function (48.4%).

Conclusion: Despite their extensive use and costs, questions around optimal use of BMAs still exist. Practice varies according to patient insurance coverage. However, most physicians are de-escalating BMAs. There is interest amongst clinicians in performing trials of de-escalation, especially after 2 years of treatment.

1. Introduction

Despite advances in adjuvant therapies, bone remains the most common site of metastases from breast and prostate cancer [1–4]. Patients with bone metastases can suffer pain, reduced health-related quality of life and function, and increased mortality [5–8]. In addition, they can experience skeletal-related events (SREs), which include the need for surgery or radiotherapy to bone, pathological fracture, spinal cord compression, or hypercalcemia. Our own single institution data has shown that 60–70% of breast and prostate cancer patients with bone metastasis experience at least one SRE during the course of their disease [7].

Based on several randomized controlled trials, bone-modifying agents (BMAs) such as bisphosphonates, including pamidronate and zoledronate, and Receptor Activator of Nuclear factor Kappa-B Ligand (RANKL) inhibitors such as denosumab, reduce the incidence of SREs and delay the time to their onset [9–15]. These agents have therefore become an established international stan-

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dard of care in the treatment of breast cancer and castration-resistant prostate cancer (CRPC) patients with bone metastases [16–21]. Despite their widespread use, many questions still exist around the optimal use of BMA, especially after 2 years of administration, where very little prospective data exists. Specifically, our group recently published a systematic review showing that data on the use of BMA beyond 2 years is largely retrospective, and that only two studies reported prospective, non-randomized data on the extended use of BMA [22,23,29]. These questions have become increasingly important as the development of more effective anti-cancer therapies has likely reduced the impact of BMAs on SSE rates. Over the last decade, trials have also evaluated less frequent administration (so called, de-escalation) of pamidronate, zoledronate and denosumab, and did not demonstrate a significantly negative impact on SRE rate [24–26]. Based on these studies, current evidence-based guidelines recommend zoledronate every 4 or 12 weeks or denosumab every 4 weeks [16,27].

Given the rapid evolution of BMA use and concern about variability in clinical practice, a survey targeting Canadian oncologists was conducted to identify current practices, the perception of long-term impact of BMA use, attitude towards BMA de-escalation (e.g., from every 4 weeks to every 12 weeks), and concerns regarding further BMA de-escalation after 2 years of use. This 2-year timeframe is important as some data suggests that the benefit of continuing BMA for over two years likely decreases as the incidence of SRE/SSEs falls with time, while the risk of developing BMA-related toxicities such as osteonecrosis of the jaw increases [22,28,29]. Although many trials historically used SRE as the primary study endpoint, the survey will instead ask about symptomatic skeletal events (SSEs), which modifies the SRE definition to include only symptomatic pathological fractures and omits asymptomatic hypercalcemia, or sometimes hypercalcemia altogether. We felt that SSE is a more clinically relevant endpoint since the goal of using BMA for bone metastases is to improve patient symptoms and health-related quality of life. The information obtained from the survey will help devise a pragmatic clinical trial to answer these questions and to ensure that trial results will have a clinical impact on patient care.

2. Materials and methods

2.1. Survey development

The survey was designed by a multidisciplinary team with established expertise in survey development and performance. The survey was pilot tested on a limited number of oncologists (MZA, TN) and one non-healthcare professional (LV) before launch. The target population was oncology clinicians across all 10 provinces in Canada who routinely administered BMAs for patients with bone metastases from breast cancer or CRPC. The first section of the survey was devised to collect pertinent demographic information on the respondents [tumor site treated, oncology subspecialty, province of practice]. The second section was designed to collect information on physician practice patterns (choice of BMA in the context of funding rules, preferred frequency of administration, and de-escalation strategies) in a Canadian context. As coverage for BMA varied across provinces, questions around routine practice were divided into those for patients with third party private insurance (where denosumab is funded for both breast and prostate cancer patients) and those without such insurance. In many provinces, denosumab is funded for prostate cancer but not breast cancer. In the third section, respondents were asked about their opinion on the value of continuing BMA for more than 2 years, their perception of SSE risk and risk of osteonecrosis of the jaw (ONJ) after more than 2 years of BMA therapy. In the fourth section, respondents were presented with different scenarios of BMA de-escalation after 2 years of therapy and asked about the clinical relevance of a randomized trial that compared such a de-escalation with the current standard. They were then asked for their opinion on an acceptable alternative primary study endpoint that could inform a change in their practice if a study of SRE or SSE as the primary endpoint was not feasible. The survey is shown in Appendix 1.

2.2. Survey implementation

The investigators have access to a collection of publicly available email addresses which were used in previous surveys of this type. The online survey was run using Microsoft Forms from the designated research coordinator's secure account within the Ottawa Hospital Research Institute. The survey was initiated on 19 May 2020 and remained open until 22 June 2020. Physicians were sent an invitation to complete the survey, a link to the electronic survey as well as an information sheet for the study. Another reminder notice was sent to participants two weeks later. The survey was approved by the Ontario Cancer Research Ethics Board (OCREB).

2.3. Data analysis

All of the data was summarized descriptively. The frequency of each answer choice was tabulated as a proportion of the total number of respondents for that category (e.g. physician tumor site subgroup). Data were analyzed using SPSS v.25.

3. Results

3.1. Physician demographics

The electronic survey was sent out to 334 physicians; 39 invitees were not eligible (maternity leave, no longer treating breast or prostate cancer, retired, or e-mail address invalid). A total of 65 eligible invitees responded; response rate was 22% of all eligible physicians. Of the eligible respondents (n = 65), 35 treated breast cancer [100% medical oncologists (MO)], 25 treated prostate cancer [76% MO, 16% radiation oncologists (RO), 8% other], and 5 treated both (80% MO, 20% other) (Table 1).

Table 1
Physician Demographics.

Total # responders/Total # contacted 65/295 (22%)	
Specialty	
Medical oncologist	58 (85.3%)
Radiation oncologist	7 (10.3%)
Urologist	2 (3%)
Internist doing oncology	1 (1.5%)
Province of practice	
Alberta	8 (11.8%)
British Columbia	4 (5.9%)
Manitoba	3 (4.4%)
New Brunswick	1 (1.5%)
Nova Scotia	3 (4.4%)
Ontario	45 (66.2%)
Quebec	3 (4.4%)
Saskatchewan	1 (1.5%)
Clinical population treated	
Breast cancer	35 (51.5%)
Prostate cancer	25 (36.8%)
Both	5 (7.4%)

3.2. Bone-targeted agent use in Canadian practice for newly diagnosed bone metastases

3.2.1. Patients with third party insurance:

Respondents were asked about their initial BMA regimen of choice for patients with newly diagnosed bone metastases from breast cancer or CRPC with no limitations in drug coverage. For breast cancer, physicians most commonly used denosumab q4wks for 3–4 months followed by a de-escalation to q12wks [13/40 (32.5%)], zoledronate q12wks [8/40 (20%)] and denosumab q4wks [7/40 (17.5%)]. For prostate cancer, physicians most commonly used denosumab q4wks [14/25 (56%)], denosumab q4wks for 3–4 months followed by a de-escalation to q12wks [7/25 (28%)], and zoledronate q12wks [2/25 (8%)] (Figs. 1a and 1b).

4. Patients without third party insurance:

Respondents were asked about their initial BMA regimen of choice for patients with newly diagnosed bone metastases from breast cancer or castration-resistant prostate cancer (CRPC) with provincial insurance coverage only (i.e., no third-party health insurance). For breast cancer, physicians most commonly used zoledronate q4wks for 3–4 months followed by de-escalation to q12wks [14/40 (35%)] and zoledronate q12wks [12/40 (30%)]. For prostate cancer, physicians most commonly used denosumab q4wks [11/25 (44%)], denosumab q4wks for 3–4 months, followed by a de-escalation to q12wks [7/25 (28%)], and zoledronate q12wks [3/25 (12%)] (Figs. 1a and 1b).

4.1. De-escalation of bone modifying agents.

Respondents were asked whether they de-escalated BMA therapy routinely (i.e. administer BMA every 12 weeks instead of every 4 weeks). Among physicians that treated breast cancer, 33/40 (82.5%) routinely de-escalated BMA, with the most common approaches being de-escalation from the start of treatment [9/33 (27.3%)], or after 3 months [7/33 (21.2%)], 6 months [6/33 (18.2%)], and 12 months [5/33 (15.2%)] of treatment. For prostate cancer, 12/25 (48%) physicians routinely de-escalated BMA, with the most common approaches being de-escalation after 3 months [7/12 (58.3%)] and 6 months [2/12 (16.7%)] of treatment (Table 2).

4.2. Perception of long-term impact of bone-modifying agents: Symptomatic skeletal events (SSEs) and risk of osteonecrosis of the jaw (ONJ)

The perceived risk of developing an SSE in patients with bone metastases from breast cancer after 2 years of BMA use (i.e., risk of SSE in the third year) was up to 5% in 7/40 (17.5%) of respondents, more than 5% and up to 10% in 13/40 (32.5%) of respondents, more than 10% and up to 15% in 9/40 (22.5%) of respondents, more than 20% and up to 25% in 1/40 (2.5%) of respondents, and more

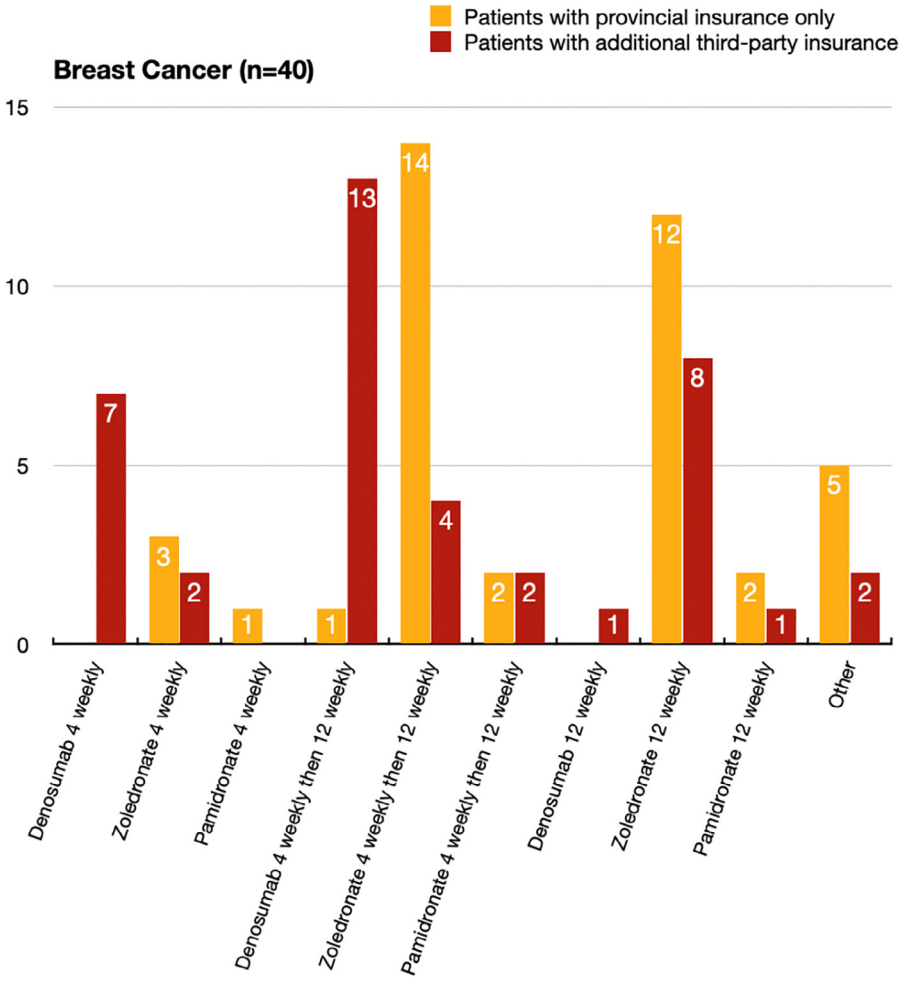

Fig. 1a. Physician preference of bone modifying agent regimen for breast cancer patients with newly diagnosed bone metastases.

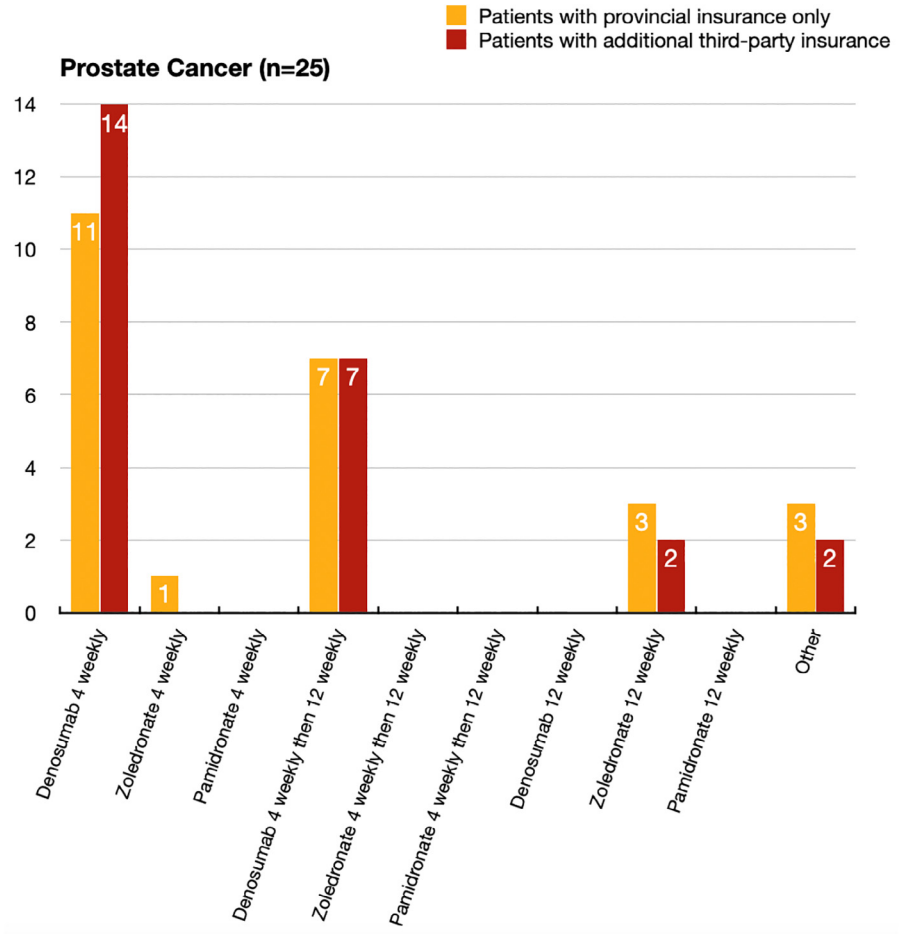

Fig. 1b. Physician preference of bone modifying agent regimen for prostate cancer patients with newly diagnosed bone metastases.

Table 2
De-escalation of bone modifying agent for newly diagnosed metastatic bone disease.

Respondents who routinely de-escalate bone modifying agent in the first 2 years	
Physicians who treat breast cancer (n = 40)	33 (82.5%)
Physicians who treat prostate cancer (n = 25)	12 (48%)

Timing of de-escalation of bone modifying agent in the first 2 years	Breast cancer (n = 33)	Prostate cancer (n = 12)
From the start of BMA treatment	9 (27.3%)	0 (0%)
After 3 months	7 (21.2%)	7 (58.3%)
After 6 months	6 (18.2%)	2 (16.7%)
After 1 year	5 (15.2%)	1 (8.4%)
After 2 year of 4-weekly therapy	1 (3%)	1 (8.4%)
Other	5 (15.2%)	1 (8.4%)

than 25% in 1/40 (2.5%) of respondents; 9/40 (22.5%) of respondents were unsure.

The perceived risk of developing an SSE in patients with bone metastases from prostate cancer after 2 years of BMA use (i.e., risk of SSE in the third year) was up to 5% in 7/25 (28%) of respondents, more than 5% and up to 10% in 4/25 (16%) of respondents, more than 10% and up to 15% in 6/25 (24%) of respondents, more than 20% and up to 25% in 3/25 (12%) of respondents, and more than 25% in 0/25 (0%) of respondents; 5/25 (20%) of respondents were unsure.

Respondents were asked about the risk of ONJ per patient-year after 2 years of BMA. Overall, combining responses from breast and prostate cancer physicians, denosumab was most commonly associated with a 2% ONJ risk [17/64 (26.6%)], zoledronic acid was most commonly associated with a 1% ONJ risk [18/64 (28.1%)], and pamidronate was most commonly associated with a 1% ONJ risk [16/38 (42%)] (Fig. 2).

4.3. Potential future trials of de-escalated therapy after 2 years of bone-modifying agent therapy

Respondents were asked for their views on the role of continuing BMA for longer than 2 years, the clinical relevance of conducting de-escalation trials after 2 years of prior BMA treatment, and the relevance of various potential study endpoints to facilitate the design of practice-changing trials.

Among physicians who treated breast cancer, 11/40 (27.5%) felt that the benefits of continuing BMA therapy outweighed the potential harms after 2 years of BMA therapy, while 5/40 (12.5%) felt there was no benefit and 24/40 (60%) were unsure of the benefit. Among physicians who treated prostate cancer, 9/25 (36%) felt that the benefits of continuing BMA therapy outweighed the potential harms after 2 years of BMA therapy, while 4/25 (16%) felt there was no benefit and 12/25 (48%) were unsure of the benefit

Respondents were asked if after 2 years of BMA treatment, whether a randomized study of 12 weekly BMA versus 24 weekly BMA (or stopping BMA) would be important for patients with bone metastases from breast cancer or CRPC: 52% of respondents thought a study comparing 12-weekly zoledronate (or pamidro-

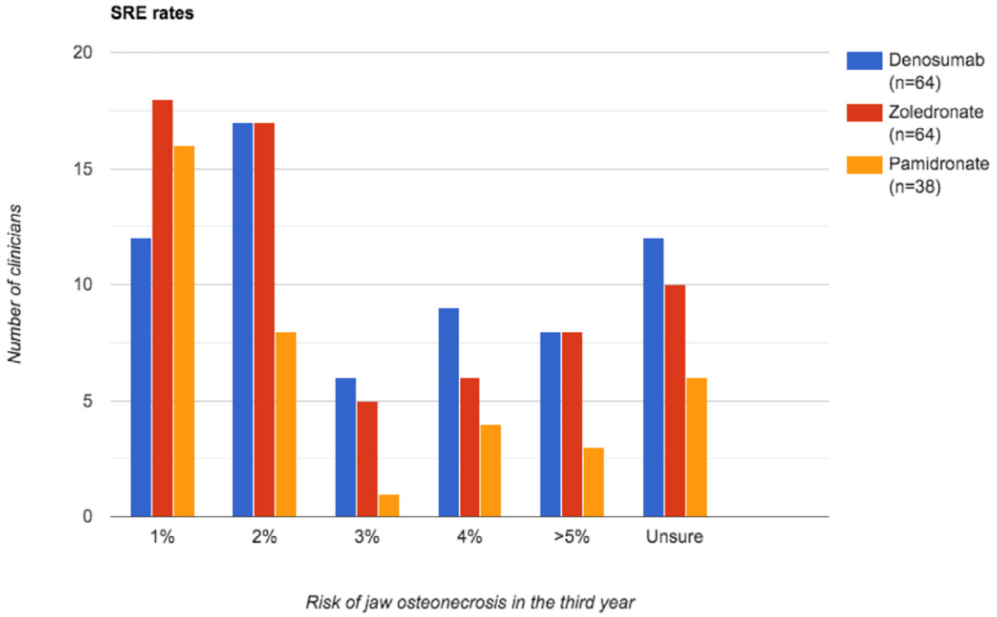

Fig. 2. Perception of risk of osteonecrosis of the jaw (ONJ) after 2 years of bone modifying agent treatment.

nate) versus 24-weekly would be clinically important while 67% thought that comparing 12 weekly zoledronate (or pamidronate) versus stopping zoledronate (or pamidronate) would be clinically important. Regarding denosumab, 55% of respondents thought a study comparing 12-weekly denosumab versus 24-weekly would be clinically important while 75% thought a study comparing 12 weekly denosumab versus stopping denosumab would be clinically important (Fig. 3).

After 2 years of BMA therapy, when asked what increase in the proportion of patients experiencing an SSE in 1 year would be tolerated in the de-escalation arm relative to the standard arm to consider changing their practice to a de-escalated BMA schedule, 2/65 (3%) suggested <1% increase, 41/65 (63%) suggested <5% increase, 15/65 (23%) suggested <10%, 0/65 (0%) suggested <20%, and 7/65 (10%) were unsure.

Respondents were asked about their opinion of an alternative acceptable primary endpoint if using SSE rate as the primary endpoint was not feasible given that such a study would likely require thousands of patients. For respondents who treated breast cancer, 25/39 (64.1%) suggested BMA toxicity rate, 19/39 (48.7%) suggested pain as measured by validated scales, 19/39 (48.7%) suggested physical function as measured by validated health-related quality of life scales, 16/39 (41.0%) suggested cost-utility/cost-effectiveness and 15/39 (38.5%) felt SSE would be the only acceptable primary endpoint to convince a change in their practice.

For respondents who treated prostate cancer, 18/25 (72%) suggested BMA toxicity rate, 11/25 (44%) suggested pain as measured by validated scales, 12/25 (48%) suggested physical function as measured by validated health-related quality of life scales, 4/25 (16%) suggested cost-utility/cost-effectiveness and 4/26 (16%) felt SSE would be the only acceptable primary endpoint to convince a change in their practice (Table 3).

5. Discussion

Despite the widespread use of BMAs in the care of patients with bone metastases from breast cancer and CRPC, the optimum schedule, duration, and type of bisphosphonate therapy remain unknown [30]. This survey was devised to gain an understanding of current Canadian prescribing patterns of bone-modifying agents. The choice of BMA was dependent on funding available to patients. Zoledronate was the most commonly used BMA in breast cancer patients without third party insurance whereas denosumab was the most common BMA choice for breast cancer with third party insurance and for CRPC regardless of funding since public funding is available for CRPC in many provinces. Physicians most often de-escalated BMA therapy from every 4 weeks to every 12 weeks within the first 3–4 months of BMA treatment. Regardless, there remains substantial variability in prescribing patterns. For example, contrary to our survey findings, a recently published cross-sectional survey of 86 oncologists in Sweden reported that only 8.1% (7/86) of oncologists reduced BMA treatment to every 12 weeks after the first 3 months of BMA therapy and only 3.4% (3/86) oncologists initiated BMA as a 12-weekly regimen. Most of the respondents in this survey (69.7%) did not consider de-escalation at least until 2 years of BMA therapy. Interestingly, the same study reported that the incidence of bone complications was the same in both the BMA-treated and untreated patient groups and that there was no difference in SRE rate between patients categorized as being at high or low risk of bone complications [31]. This data supports the idea that it is safe to de-escalate BMA to every 12 weeks in the first two years. ZOOM and OPTIMIZE-2 were randomized studies that suggested reducing BMA treatment to every 12 weeks after the first year of treatment with BMA every 4 weeks is safe [25,26]. REaCT BTA took this a step further and showed that using a 12-weekly regimen of bisphosphonate or denosumab from the start of treatment was non-inferior to BMA every 4 weeks in terms of physical functioning [32]. Although this study has possibly changed practice for many oncologists, especially for reducing the frequency of intravenous bisphosphonates early, we anticipate that the much larger SAKK 96/12 REDUSE study will definitively answer whether it is safe to reduce the frequency of denosumab early on in treatment [33].

The decision of whether to extend BMA therapy beyond 2 years, an area without any evidence base from prospective randomized studies, is typically based on the anticipated clinical benefit and potential toxicity from continuing treatment. In this survey, there was no clear consensus on the risk of SSE in the third year of BMA administration. However, most physicians suggested SSE risk to be 15% or less [72.5% (29/40) and 68% (17/25) from breast and

prostate cancer physicians, respectively]. This is compatible to what was reported in a systematic review of 12 studies that examined BMA efficacy and toxicity after more than 2 years of therapy [22]. Similarly, there was no consensus regarding the risk of ONJ in the third year of BMA administration. However, respondents most often perceived the risk of ONJ in the third year of BMA administration to be quite low (2% for denosumab; 1% for zoledronate or pamidronate). Contrary to these results, the aforementioned systematic review found studies reporting the risk of ONJ after more than 2 years of BMA may be as high as 7% to 18%, highlighting that the perceived risk from long-term BMA administration may be underestimated [22]. The majority of breast and prostate cancer physicians in our survey were unsure of the benefit of continuing BMA therapy for more than 2 years. However, more often than not, they felt there would be benefit in continuing for longer. Certainly, in the absence of level one evidence, the decision to continue, de-escalate, or stop BMA therapy after 2 or more years needs to be customized for each patient, highlighting the need to conduct high-quality, randomized studies to examine the role of de-escalating BMA treatment in this setting.

Regarding the design of a future clinical trials geared towards studying the role of de-escalated BMA therapy after the first two years, physicians were very interested in de-escalation trials and most would even consider discontinuing therapy after two years. For this type of study, assuming that SRE or SSE was not a feasible primary endpoint, the most commonly selected alternate acceptable endpoint that would potentially change practice was if BMA toxicity was superior in the de-escalated arm. Acknowledging that ONJ is the most relevant late toxicity (24), our survey only asked about BMA toxicity as an umbrella term without specifying ONJ as a substitute study endpoint for SSE or SRE. Notably, a major challenge in conducting a non-inferiority, randomized, treatment de-escalation trial using ONJ incidence rate per year as the study endpoint is the potentially insurmountable sample size required if one were to assume the rate of ONJ is quite low. Note that survey respondents often selected more than one acceptable alternate study endpoint and other top choices included physical function (breast: 48.7%; prostate 48%) and pain (breast: 48.7%; prostate: 44%) as measured by validated scales, either of which would be more feasible endpoints to use in a randomized trial in this clinical setting. Nonetheless, there remains a need for further large, randomized trials with SSE as the primary endpoint.

As with all surveys, there is an inherent selection bias in those that responded to the survey. It is a survey of Canadian physicians, so the choice of BMA is influenced by provincial treatment-funding policies. The impact of the frequency of BMA therapy may vary based on the schedule of a patient's other systemic therapies, and we are in the process of completing a separate patient survey

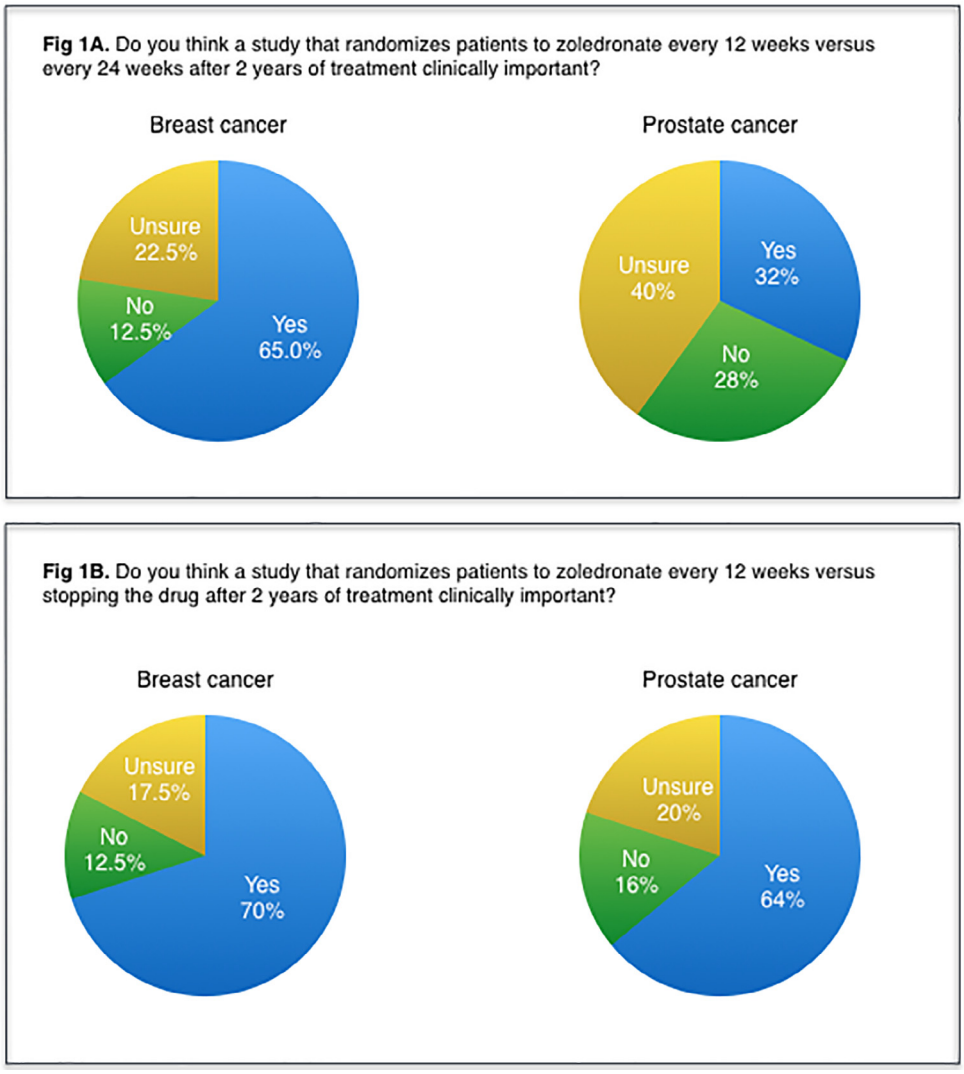

Fig. 3. Perception toward future trials of de-escalated therapy after 2 years of bone-modifying agent therapy.

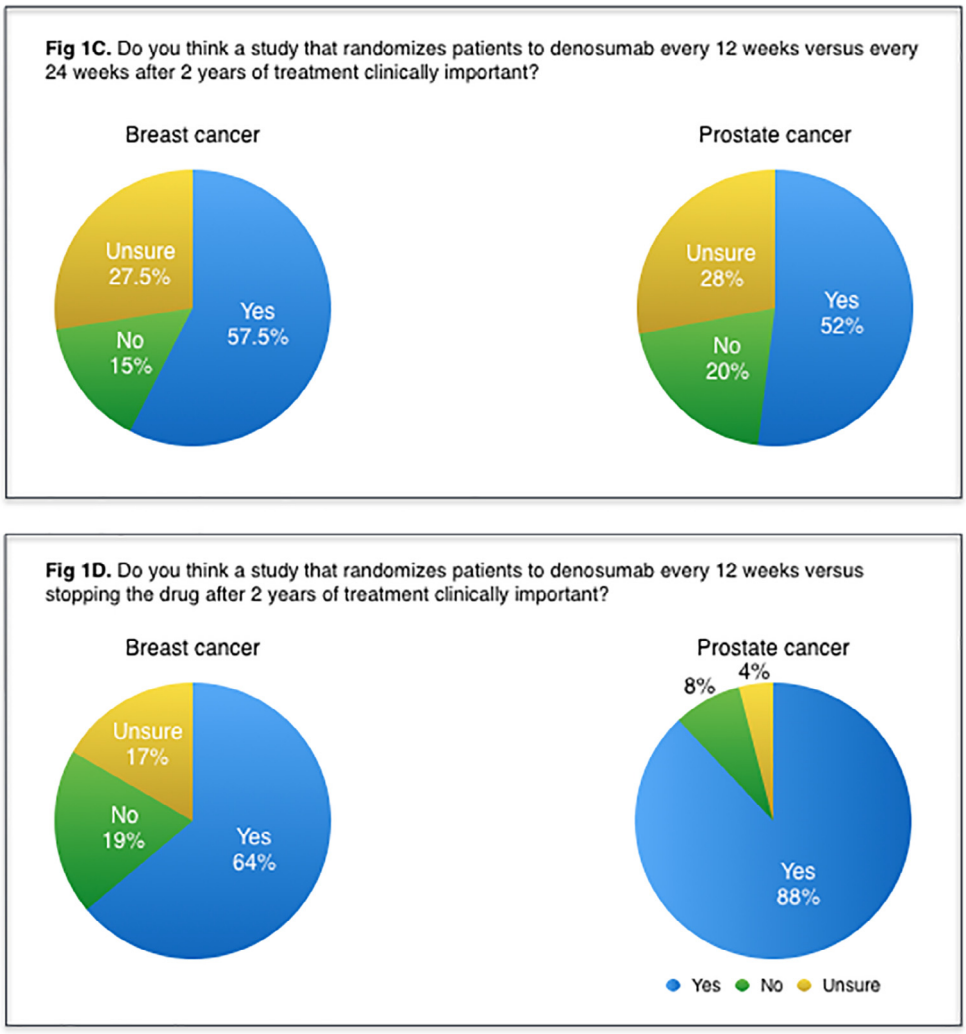

Fig. 3 (*continued*)

Table 3
Acceptable study outcomes that would lead to adopting bone modifying agent de-escalation.

Maximum acceptable increase in the rate of SSE per year in the de-escalation vs. standard schedule		
	Breast cancer (n = 40/68)	Prostate cancer (n = 25/68)
<1%	2 (5%)	0 (0%)
<5%	26 (65%)	15 (60%)
<10%	7 (17.5%)	8 32%)
Unsure	5 (12.5%)	2 (8%)
Alternative acceptable primary endpoint to conduct a non-inferiority study of BMA de-escalation that would convince you to change practice if using SSE rate as the primary endpoint is not feasible		
	Breast cancer (n = 39/68)	Prostate cancer (n = 25/68)
BMA toxicity	25 (64.1%)	18 (72%)
Pain	19 (48.7%)	11 (44%)
Physical function	19 (48.7%)	12 (48%)
Cost-utility/cost-effectiveness	16 (41.0%)	4 (16%)
SSE is the only acceptable primary endpoint	15 (38.5%)	4 (16%)

to explore these issues. The impact of the lower than expected response rate could be attributed to the short duration that the survey was open for (1 month), but probably also due to the overwhelming situation to all health care workers during the COVID-19 pandemic.

6. Conclusions

The results from this study highlight the clinical importance of addressing the role of BMA de-escalation after more than 2 years of treatment. It will serve as a useful guide in the design of future clinical trials and increase the likelihood that trial results will have a clinical impact. Given there is no robust data to estimate the expected differences between standard frequency treatment and de-escalated treatment, this feedback from BMA prescribers in a Canadian context will be of great value.

Declaration of Competing Interest

TN reports personal fees (honoraria) from ARIAD, Takeda and Boehringer-Ingelheim, outside the submitted work. BH and MC reports consulting fees from Cornerstone Research, outside the submitted work. All other authors declare no competing interests.

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Author contributions

AJM, MC, LV, GP and TN designed the study and prepared the protocol. MS and LV collected the data and coordinated the study and AJM, NT and GP did the statistical analysis. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. AJM, MC, TN and GP wrote the manuscript. All authors were involved in the critical review of the manuscript and approved the final version.

Ethics committee approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of each institution Research Ethics Board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Completion of the survey implied consent to participate. All data has been anonymized to protect the identities of subjects involved in the research.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbo.2020.100339.

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