Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Clinical Trial

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

Mark Clemons a,b,c,* , Michael Ong a , Carol Stober b , Scott Ernst d , Christopher Booth e , Christina Canil a , Mihaela Mates e , Andrew Robinson e , Phillip Blanchette d , Anil Abraham Joy f , John Hilton a,b , Olexiy Aseyev g , Gregory Pond h , Ahwon Jeong b , Brian Hutton c , Sasha Mazzarello b , Lisa Vandermeer b , Igal Kushnir a , Dean Fergusson c on behalf of the REaCT investigators

* Corresponding author. Division of Medical Oncology The Ottawa Hospital Cancer Centre, 501 Smyth Road, Ottawa, Canada. Fax: +1 613 247 3511.
E-mail address: mclemons@toh.ca (M. Clemons).

KEYWORDS
breast cancer;
prostate cancer;
bone metastasis;
pamidronate;

Abstract  Background: Optimal dosing of bone-targeted agents (BTAs), in patients with bone metastases remains an important clinical question. This trial compared 4-weekly versus 12-weekly therapy.

Patients and methods: Patients with bone metastases from breast or castration-resistant prostate cancer (CRPC), who were going to start or already on BTAs, were randomised 1:1 to 4-
The use of bone-targeted agents (BTAs), such as bisphosphonates and Receptor activator of nuclear factor kappa-B (RANK) ligand inhibitors, in patients with bone metastases from breast and castration-resistant prostate cancer (CRPC) is associated with improvements in morbidity, pain, quality of life (QoL) and skeletal-related events (SREs). They have shown no improvement in either progression-free or overall survival. As supportive care drugs, questions remain around their optimal dosing [1].

De-escalation studies with pamidronate [2], zoledronate [3-5] and denosumab [6] have shown similar efficacy outcomes across a broad range of end points in the 4-weekly and 12-weekly groups. Systematic reviews in both breast [7] and prostate cancer [8] confirmed equivalent outcomes with 4-weekly versus 12-weekly dosing. Despite these findings and evidence-based guidelines stating the efficacy of 12-weekly zoledronate [9], surveys of both patients and oncologists confirmed that significant clinical equipoise still exists with patients receiving different BTAs at different dosing intervals [10,11].

Although a comparison of SREs rates would be the preferred primary end point for studies comparing dosing intervals of BTAs, the use of this end point would require a study sample size in the thousands. However, as BTAs are supportive care interventions, health-related quality of life (HRQoL) is also important and validated patient reported outcome. In this pragmatic non-inferiority trial, we evaluated the effects of 4-versus 12-weekly dosing of three commonly used BTAs in terms of HRQL, pain, symptomatic skeletal events (SSEs) and toxicity.

1. Introduction

We conducted this pragmatic, randomised, open-label, non-inferiority trial at five Canadian centres. Patients with bone metastases from either metastatic breast or CRPC, who were either going to start or were already on BTAs (either denosumab, pamidronate, or zoledronate) were eligible. Other eligibility requirements included Eastern Cooperative Oncology Group performance status 0-2, estimated life expectancy of >12 months and able to provide verbal consent. Exclusion criteria included history of or current evidence of osteonecrosis of the jaw (ONJ), or planned radiotherapy or surgery to the bone within 4 weeks of randomisation. There were no study-mandated changes in the type of BTA the patient received, no prior maximum duration of BTA use and patients could have had prior SSEs. All patients provided verbal consent following the integrated consent model [12]. The study was approved by the Ontario Research Ethics Board and registered on clinicaltrials.gov (NCT02721433). This report was prepared following the CONSORT extension for non-inferiority trials [13].

2. Patients and methods

2.1. Study population

Eligible and consented patients were randomised in a 1:1 ratio using a permuted block design with variable block sizes of 2 and 4 to either 4-weekly or 12-weekly BTAs for 1 year via a web-based randomisation system. Stratification was based on tumour type (breast vs. CRPC) and centre. After enrolment, neither investigators nor participants were masked to treatment allocation.
2.3. Procedures

The choice of BTA (either denosumab, pamidronate and zoledronate) was made before randomisation and was left to the patient and treating physician. Patients were instructed to take calcium and vitamin D as per guidelines. As the trial was pragmatic in nature, if a patient was receiving another systemic therapy every 3 weeks and therefore randomisation to the 4-weekly BTA arm would be more inconvenient, then the BTA could be administered every 3 or 6 weeks.

End point data were collected from self-completed patient questionnaires European Organisation for Research and Treatment of Cancer (EORTC)-QLQ-C30 and EORTC-QLQ-BM22) [14,15]. Study data were also obtained and verified through the patient’s electronic medical record and emails to treating physician. Patients were assessed at their usual clinic visits. No radiological assessments beyond conventional practice were mandated.

2.4. Outcomes

The primary outcome was the change in patient HRQoL scores (EORTC-QLQ-C30 Physical Subdomain) during the first year post-randomisation. This end point was chosen as it is patient-centred, clinically meaningful and validated in patients with bone metastases [15–17]. Information was collected at baseline and weeks 12, 24, 36 and 48. A decrease in the HRQL score is associated with worsening quality of life.

Secondary end points evaluated pain (BM22 pain domain), global health status (C30), SSEs and toxicity. SSEs were defined as radiotherapy to bone, new symptomatic pathological bone fractures, spinal cord compression, tumour-related orthopaedic surgery, and hypercalcaemia. Time to development of SSEs was calculated from the date of randomisation until the first date a patient experienced an SSE and presented as a cumulative incidence rate. Any patient not experiencing an SSE was censored on the last date that they were confirmed to be SSE-free. Total number of SSEs and time to subsequent on-study SSE were used to calculate the skeletal morbidity rates (SMR, mean number of SSEs per year). Adverse events, toxicity profiles and bone metastases-related hospitalisation were collected from electronic health records.

2.5. Sample size and statistical analysis

It was assumed there would be no difference between the 12-weekly and 4-weekly treatment arms, and a non-inferiority bound of 5 points on the C30 Physical Subdomain at 48 weeks used. This 5-point inferiority margin has previously been shown to be clinically meaningful in patients receiving BTAs [15–17]. Furthermore, a 5-point change in the C30 was expected to be equivalent to a change of roughly 0.5 standard deviations, which is often used as a guideline to measure a clinically important difference. To have 80% statistical power in ensuring the lower limit of a one-sided 95% confidence interval (CI) (or equivalently a 90% two-sided CI) will be above the non-inferiority limit, a minimum of 224 patients was required. To allow for an expected 10% non-compliance rate and account for stratification, enrolment of 250 total patients was planned. Additional statistical power would be realised through the use of a repeated measures analysis.

2.6. Analytic plan

Baseline characteristics are summarised using means and standard deviations (continuous measures) or proportions (categorical data). As a non-inferiority study, the primary analysis was based on a per protocol data set, defined as those patients who completed all 48 weeks of allocated treatment. Supportive analyses were conducted after the intention-to-treat principle, using data from all patients in accordance with the allocated treatment, irrespective of missing or incomplete data. The mean difference in the C30 Physical Subdomain calculated between treatment groups using repeated-measure analysis of variance was used as the primary analysis. Secondary analyses were performed looking at the difference between interventions for different C30 domains at each time point separately.

Secondary outcomes were compared using Fisher’s exact tests, Cochran-Armitage test for trends and Wilcoxon rank sum tests as appropriate. Relative risk (dichotomous) and mean differences (continuous) along with their 95% CIs were calculated and presented. Subgroup analyses were performed to explore differences based on disease, type of BTA and prior exposure; however, there was insufficient power available to perform definitive analyses within subgroups, and these are considered exploratory analyses only.

All analyses were performed using SAS, version 9.2 (SAS Institute, North Carolina, USA). Except where indicated, all tests were two-sided at the α = 0.05 level of significance.

3. Results

Between August 3, 2016 and June 5, 2018, 263 patients were enrolled and 133 (50.6%) randomised to 4-weekly and 130 (49.4%) to 12-weekly therapy (Fig. 1, CONSORT diagram). Baseline characteristics are in shown in Table 1, where 60.8% (160) of patients had breast cancer and 39.2% (103) of patients had CRPC. Median patient age was 68 (interquartile range: 57 to 75). Patients received denosumab (n = 148, 56.3%), zoledronate (n = 63, 24.0%) and pamidronate (n = 52, 19.8%). There were more patients with CRPC on denosumab
Amongst all the randomised patients, 136 (51.7%) were bone-agent naïve. Amongst patients with prostate cancer, 78% were BTA-naïve in the 12-weekly cohort, whereas 62% were BTA-naïve in the 4-weekly cohort. This difference was not statistically significant (p-value = 0.086). As baseline anti-cancer treatments could affect HRQoL, data are presented for the highest accruing site (Table 1), and these were balanced. For patients at this site who were receiving trastuzumab (and the protocol allowed patients randomised to 4-weekly BTA to receive their BTA every 3 or 6 weeks for convenience), BTAs were administered 3-weekly (n = 1), 4-weekly (n = 4), 6-weekly (n = 3) and one patient was treated every 12-weeks due to physician error. Just more than three-fourth of patients (201) completed the study at 1 year, reasons for attrition were death (54), withdrawal or refusal (5) and lost to follow-up (3).

Across all time points, the mean (sd) physical functioning score was 75.0 (1.3) for patients in the 4-weekly, and 73.8 (1.3) for the 12-weekly arm, resulting in a mean (sd) difference of 1.2 (1.4). The lower bound for the one-sided, 95% CI is 3.6, which was greater than the a priori defined boundary for declaring non-inferiority. Therefore, the 12-weekly was concluded to be non-inferior to the 4-weekly arm in terms of physical functioning for the first 48 weeks after treatment initiation (Online Supplemental Table 1).
Table 1
Patient baseline disease and treatment characteristics. Values are n (%) unless otherwise indicated.

|                                | 4-weekly BTA (n = 133) | 12-weekly BTA (n = 130) |
|--------------------------------|------------------------|-------------------------|
| Age, median, (range)           | 67 (26, 97)            | 68 (30, 92)             |
| Female                         | 81 (60.9)              | 79 (60.8)               |
| Mean baseline serum creatinine (SD), mg/dL | 0.83 (0.22)           | 0.90 (0.30)            |
| Disease characteristics        |                        |                         |
| Cancer type                    |                        |                         |
| Breast                         | 81 (60.9)              | 79 (60.8)               |
| CRPC                           | 52 (39.1)              | 51 (39.2)               |
| Median months from initial bone metastases diagnosis to randomisation (range) | 15.3 (93.5) | 7.0 (0, 86.8) |
| N (%) <3 months                | 31 (23.3)              | 42 (32.3)               |
| 3–5.9 months                   | 10 (7.5)               | 19 (14.6)               |
| 6–11.9 months                  | 13 (9.8)               | 13 (10.0)               |
| 12–23.9 months                 | 36 (27.1)              | 21 (16.2)               |
| >24 months                     | 43 (32.3)              | 35 (26.9)               |
| Median months from initial bone metastases diagnosis to randomisation (range), prostate | 22.4 (1.0) | 19.2 (0, 86.8) |
| N (%) <3 months                | 1 (1.9)                | 9 (17.7)                |
| 3–5.9 months                   | 5 (9.6)                | 3 (5.9)                 |
| 6–11.9 months                  | 5 (9.6)                | 7 (13.7)                |
| 12–23.9 months                 | 18 (34.6)              | 11 (21.6)               |
| >24 months                     | 23 (44.2)              | 21 (41.2)               |
| Median months from initial bone metastases diagnosis to randomisation (range), breast | 8.9 (93.5) | 4.1 (0, 71.8) |
| N (%) <3 months                | 30 (37.0)              | 33 (41.8)               |
| 3–5.9 months                   | 5 (6.2)                | 16 (20.3)               |
| 6–11.9 months                  | 8 (9.9)                | 6 (7.6)                 |
| 12–23.9 months                 | 18 (22.2)              | 10 (12.7)               |
| >24 months                     | 20 (24.7)              | 14 (17.7)               |
| Prior SSEs                     | 60 (45.1)              | 54 (41.5)               |
| Radiotherapy to bone for reduction in fracture risk | 0 (0.0) | 2 (3.7) |
| Radiotherapy to bone for pain   | 51 (85.0)              | 46 (85.2)               |
| Radiotherapy to bone, reason other | 1 (1.7)            | 2 (3.7)                 |
| Pathological fracture           | 6 (10.0)               | 6 (11.1)                |
| Surgery to bone                | 3 (5.0)                | 2 (3.7)                 |
| Spinal cord compression         | 4 (6.7)                | 3 (5.6)                 |
| Hypercalcaemia                 | 1 (1.7)                | 1 (1.9)                 |

Treatment characteristics

| Type of BTA                  | Denosumab | Pamidronate | Zoledronate | Prior use of parenteral BTA |
|------------------------------|-----------|-------------|-------------|-----------------------------|
| Denosumab                    | 77 (57.9) | 25 (18.8)   | 31 (23.3)   | 73 (54.9)                   |
| Pamidronate                  | 25 (18.8) | 27 (20.8)   | 32 (24.6)   | 54 (11.5)                   |
| Zoledronate                  | 31 (23.3) | 27 (20.8)   | 32 (24.6)   | 54 (11.5)                   |
| Mean (sd)                    | 4.5 (8.9) | 5.0 (8.5)   |             |                             |

SSE data are presented in Table 2 with the 1-year cumulative incidence rate presented in Fig. 2, whereas SSE-free survival was 79.1% (95% CI: 71.0 to 85.2) and 72.4% (95% CI: 63.5 to 79.5) at 1-year in the 4- and 12-weekly groups, respectively (p = 0.31; Fig. 3). No differences were noted between groups by the type of BTA (p-value = 0.65 for all patients combined, or p-value = 0.92 and 0.32 within patients with breast and CRPC cohorts, respectively) or whether the patients were BTA-naïve or pre-treated or amongst patients with CRPC. Among patients with breast cancer, the 4-weekly group had a greater SSE-free survival of 82.2% (95% CI: 71.7 to 89.1) than the 12-weekly group with 68.0% (95% CI: 56.1 to 77.3), which approached but did not attain statistical significance (p = 0.051).
A total of 44 SSEs were experienced by patients in the 12-weekly arm during the 1-year follow-up, with a mean of 0.34 SSEs per patient and maximum 5 per patient. This was similar in the 4-weekly arm, where a total of 44 SSEs were experienced, with a mean of 0.33 SSEs per patient and maximum 5 per patient.

The physician reported incidence of ONJ, renal impairment, and bone metastasis–related hospitalisations were similar between the groups (Online Supplemental Table 3). Biochemical hypocalcemia was evaluated in patients with CRPC treated with denosumab (n = 51) at the Ottawa Hospital. There was no significant difference in hypocalcemia rate between the 2 groups. Eight patients (31%) treated with 4-weekly denosumab and 10 patients (40%) treated with 12-weekly had hypocalcemia.

There was a change in BTA (including change in frequency or agent or discontinuation of BTA altogether) in 27 (20.8%) patients in the 4-weekly compared with 49 (36.9%) patients in the 12-weekly group. Frequency of drug administration was changed in 11 patients (8.5%) in the 12-weekly group changing to 4-weekly therapy, whereas 18 patients (13.5%) in the 4-weekly group changed to 12-weekly dosing (Fig. 1, CONSORT diagram).

4. Discussion
This is the first prospective randomised, open label, clinical trial involving patients with bone metastases from either breast or CRPC, comparing 4-weekly versus 12-weekly dosing of three commonly used BTAs. The change in physical function met our definition of non-inferiority looking at the primary outcome of the physical function domain. No statistically significant differences in secondary outcomes were observed between patients on the two different intervention arms. These results are consistent with those previously reported for de-escalating zoledronate and add to the literature about the acceptability of de-escalating Table 2
Clinical end point data.

| Primary end point | 4-weekly | 12-weekly | p-value | Estimated difference (95% CI) |
|-------------------|----------|-----------|---------|------------------------------|
| Mean (std dev) change in physical functioning across all time points | −6.4 (1.3) | −4.5 (1.3) | 0.20 | −1.9 (−4.8, 1.0) |

Table 3
EORTC-QLQ-C30 Functional Domain (Physical Subdomain) by study group, tumour type and bone-targeted agent. Values are mean (sd) change in physical subdomain score from baseline to week 48.

| | 4-weekly | 12-weekly | p-value | Estimated difference (95% CI) |
|-----------------|----------|-----------|---------|------------------------------|
| All             | −3.7 (22.7) | −4.7 (24.1) | 0.69 | −1.0 (−8.1, 6.0) |
| BTA-naïve       | −3.9 (27.4) | −10.6 (27.8) | 0.46 | −6.7 (−18.8, 5.3) |
| Prior exposure  | −3.5 (19.0) | 3.1 (15.1) | 0.071 | 6.6 (−0.6, 13.8) |
| Denosumab       | −5.8 (23.9) | −4.0 (26.1) | 0.28 | 1.7 (−8.3, 11.8) |
| Pamidronate     | 2.1 (23.7) | −12.1 (23.8) | 0.13 | −14.2 (−30.6, 2.2) |
| Zoledronate     | −3.7 (18.5) | 0.0 (18.2) | 0.59 | 3.7 (−8.1, 15.4) |
| Breast cancer   | 1.1 (21.5) | −5.4 (24.6) | 0.40 | −6.5 (−15.1, 2.2) |
| Prostate cancer | −14.5 (21.9) | −3.5 (23.5) | 0.052 | 11.0 (−0.9, 23.0) |

EORTC = European Organisation for Research and Treatment of Cancer, CI = confidence interval.

a Wilcoxon rank sum tests.
denosumab and pamidronate. This data, in addition to systematic reviews in both breast [7] and prostate cancer [8], indicate no statistically significant evidence against the suggestion that de-escalation of BTA is a reasonable treatment option. These findings are especially important at the moment due to the COVID-19 pandemic, when both patients and physicians are trying to safely reduce the number of visits patients make to healthcare providers.

The observed difference in SSE rates between the two study arms is notable. Previous studies have shown similar rates of SREs and SSEs between 4-weekly versus 12-weekly dosing of pamidronate [2,4], zoledronate [3,5,18] and denosumab [6]. Prior evidence from systematic reviews of de-escalation in both breast [7] and prostate [8] populations showed no significant difference in SSE rates. To date the largest data set is from three trials evaluating the de-escalation of zoledronate in patients with breast cancer [3,5,18] and showed no significant difference in SSE rates. This is reflected in recommendations from evidence-based guideline groups [19]. In the current trial, the 1-year cumulative incidence rate of SSE was 7.6% (95% CI: 4.3 to 10.9) and 16.6% (95% CI: 12.0 to 21.2), whereas the 1-year SSE-free survival was 79.1% (95% CI: 71.0 to 85.2) and 72.4% (95% CI: 63.5 to 79.5) in the 4-weekly and 12-weekly arms, respectively. Despite these observed differences, none of these were statistically significant. Although the study was not powered to show a difference in SSEs and these results are not incompatible with chance results. Given the additional evidence from other trials indicating no difference in SSE rates, it is believed that the observed numerical differences in SSE rates between 4-week and 12-week BTA is due to chance; however, further evidence is required to confirm this hypothesis.

Our rate of asymptomatic hypocalcemia was similar to that recently reported [20], but we did not detect any difference between treatment arms in this small sample size. As this was a pragmatic trial, patients did not undergo extensive toxicity assessments, and therefore the incidence of ONJ of 2 of 263 (0.76%) patients and renal dysfunction of 8 of 263 (3.0%) patients is lower than previous trials. Although toxicity rates were similar, patients in the 4-weekly group were less likely to stay on the randomised arm and often changed to a de-escalated schedule.

This study has both strengths and limitations. Although there is considerable heterogeneity in the study subgroups (2 different tumour types, 3 different drugs, 2 different settings with patients pre-treated with BTA and BTA-naive), the study was designed to be broadly applicable to real-world practice by including patients with breast and CRPC. These differences in baseline characteristics could have led to differences in the results. For example, patients who have been on BTAs might be assumed to have a different risk profile for SSEs compared with BTA-naive subjects. The pragmatic nature of the trial with very few restrictive inclusion criteria also means that the study population more readily reflects that in clinical practice. The pragmatic nature did however mean that factors like burden of bone metastases (e.g. <3 bone metastases vs 3–10 metastases vs > 10 or similar) was not available for the analysis as this level of data is not routinely collected at the study sites. This reality of real-world practice is noticeable in the number of patients who died during the study period (n = 54), as well as the number of patients who changed from 12-weekly to 4-weekly dosing (8.5%) and from 4-weekly to 12-weekly (13.5%) dosing (refer Consort Fig. 1). Although the
sample size calculation included a 10% adjustment for patient attrition (for a total sample size of 250 patients) and 263 patients were accrued, it is clear that in reality in the setting of a real-world trial in patients with metastatic cancer that this value should have been higher. Use of HRQoL was also important as ultimately with any palliative intervention, we need to ensure quality of life of our patients.

The study was designed as open-label because the use of sham to enable double-blinding would have added considerable expense and likely have hindered accrual. The sample size was based on HRQoL analysis as the primary end point. Use of SSE as the primary end point would have significantly increased the sample size, the duration and the cost of the trial to such an extent to make it unlikely to ever occur in our current research funding environment. As BTAs are supportive care interventions, HRQoL is also important and validated patent reported outcome. A challenge with all studies is the choice of HRQoL score to use, especially as some are long for patients to complete and missing data due to patient ‘questionnaire fatigue’ becomes very challenging. Although several bone metastasis–specific tools exist, we felt as the QLC-30 has been validated in patients receiving BTAs [15,21] (as well as radiotherapy) [22] and its relative ease of completion, that this tool would enable us to achieve the goals of the study. Another limitation could be viewed as the inclusion of hypercalcaemia of malignancy as an SSE in the present study. However, as hypercalcaemia can lead to hospitalisations and incurs costs to both the patient and the healthcare system, we felt it was important to include it as an end point. Given the lack of any clinically meaningful difference in the primary analysis, even with greater sample size, it is highly unlikely to affect the study results substantially. Finally, the study follow-up was only for 1 year; however the protocol has been updated to allow patients to remain on study for 2 years, which will be analysed at a later date.

5. Conclusion

In this pragmatically designed randomised clinical trial for metastatic breast or CRPC, 12-weekly BTAs were non-inferior to 4-weekly BTAs for our HRQoL primary outcome. This trial’s results are consistent with those previously reported for de-escalating zoledronate and add to the literature about the acceptability of de-escalating denosumab and pamidronate. The standard incorporation of 12-weekly dosing of BTAs into routine clinical practice could substantially benefit both patients and the healthcare system. While awaiting the results of the REDUSE trial [23] which will definitively answer the question of de-escalating 4-weekly to 12-weekly denosumab in our opinion, de-escalation of all commonly used bone-targeted agents is a reasonable clinical decision.

Author contributions

M.C., A.R., S.M., L.V. and D.F. designed the study and prepared the protocol. M.C., M.O., C.S., S.E., C.B., C.C., M.M., A.R., P.B., A.A.J., J.H., O.A. and I.K. collected the data. M.C. acted as principal investigator and S.M. was the study coordinator. G.P. did the statistical analysis. C.S. and A.J. coordinated data entry. M.C., C.S., G.P., A.J. and L.V. wrote the manuscript. All authors were involved in the critical review of the manuscript and approved the final version.

Funding

This work was supported by the Rethinking Clinical Trials Program (REaCT), the Canadian Institute of Health Research (Patient Oriented Research grant), Cancer Care Ontario – Government of Ontario (Clinical Programs and Quality Initiatives grant 2017 and 2018 competitions), the Ottawa Hospital Foundation and its generous donors and the Canadian Cancer Clinical Trials Network (3CTN).

Ethics committee approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institution, the Ontario Cancer Research Ethics Board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all trial participants included in the study.

Conflict of interest statement

M.C. is a coauthor on both the American Society of Clinical Oncology – Cancer Care Ontario Focused Guideline on the role of Bone-Modifying Agents in Metastatic Breast and the UpToDate chapter on Osteoclast inhibitors for patients with bone metastases from breast, prostate, and other solid tumours. C.C. reports receiving travel, accommodation or other expenses paid or reimbursed by Amgen in the past 2 years. B.H. reports receiving consulting fees from Cornerstone Research, outside of the submitted work. All other authors declare no competing interests.

Acknowledgements

The authors are grateful for patients and their families for their assistance with this study, as well as physicians for approaching patients. Main accrual by physician was as follows: Clemons (83), Ong (21), Ernst...
(17), Booth (15), Canil (14), Mates (10), Reaume (9), Joy (9), Robinson (8), Hilton (7), Verma (7), Aseyev (6), Chan (6), Dent (6), Gertler (6), Blanchette (5) and Fernandes (5).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.08.019.

References

[1] Hutton B, Mazzarello S, Clemons M. Dosing strategies of bone-targeting agents. JAMA Intern Med 2015;175(11):1864–5.
[2] Addison CL, Bouganim N, Hilton J, Vandermeer L, Dent S, Amir E, et al. A phase II, multicentre trial evaluating the efficacy of de-escalated bisphosphonate therapy in metastatic breast cancer patients at low-risk of skeletal-related events. Breast Canc Res Treat 2014;144(3):615–24.
[3] 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):663–70.
[4] Amir E, Freedman O, Carlsson L, Dranitsaris G, Tomlinson G, et al. Randomized feasibility study of de-escalated (every 12 wk) versus standard (every 3 to 4 wk) intravenous pamidronate in women with low-risk bone metastases from breast cancer. Am J Clin Oncol 2013;36(5):436–42.
[5] 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;317(1):48–58.
[6] Lipton A, Steger GG, Figueroa J, Alvarado C, Solal-Celigny P, Body JJ, et al. Randomized active-controlled phase II study of denosumab efficacy and safety in patients with breast cancer-related bone metastases. J Clin Oncol : Off J Am Soc Clin Oncol 2007;25(28):4431–7.
[7] Awan AA, 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):465–7.
[8] Hong BY, Ibrahim MF, Fernandes R, Mazzarello S, Hutton B, Shorr R, et al. De-escalation of bone-targeted agents for metastatic prostate cancer. Curr Oncol 2016;23(1):e77–8.
[9] Dhesy-Thind S, Fletcher GG, Blanchette PS, Clemons MJ, Dillmon MS, Frank ES, et al. 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 2017;35(18):2062–81.
[10] Hutton B, Addison C, Mazzarello S, Joy AA, Bouganin N, Fergusson D, et al. De-escalated administration of bone-targeted agents in patients with breast and prostate cancer: A survey of Canadian oncologists. J Bone Oncol 2013;2(2):77–83.
[11] Hutton B, Morretto P, Emmenegger U, Mazzarello S, Kuchuk I, Addison CL, et al. Bone-targeted agent use for bone metastases from breast cancer and prostate cancer: a patient survey. J Bone Oncol 2013;2(3):105–9.
[12] Basualiman B, Awan AA, Fergusson D, Vandermeer L, Arnaout A, Hilton J, et al. Creating a pragmatic trials program for breast cancer patients: Rethinking Clinical Trials (REaCT). Breast Cancer Res Treat 2019;177:93–101.
[13] Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. Jama 2012;308(24):2594–604.
[14] Groenvold M, Klee MC, Sprangers MA, Aaronson NK. Validation of the EORTC QLQ-C30 quality of life questionnaire through combined qualitative and quantitative assessment of patient-observer agreement. J Clin Epidemiol 1997;50(4):441–50.
[15] Chow E, Hird A, Velikova G, Johnson C, Dewolff L, Bezjak A, et al. The European organisation for research and treatment of cancer quality of life questionnaire for patients with bone metastases: the EORTC QLQ-BM22. Eur J Canc 2009;45(7):1146–52. Oxford, England : 1990.
[16] Raman S, Ding K, Chow E, Meyer RM, van der Linden YM, Roos D, et al. Minimal clinically important differences in the EORTC QLQ-C30 and brief pain inventory in patients undergoing re-irradiation for painful bone metastases. Qual Life Res : Int J Qual Life Aspect Treat, Care Rehabil 2018;27(4):1089–98.
[17] Cramarossa G, Zeng L, Zhang L, Tseng L-M, Hou M-F, Fairchild A, et al. Predictive factors of overall quality of life in advanced cancer patients using EORTC QLQ-C30. Expert Rev Pharmacoecon Outcomes Res 2014;14(1):139–46.
[18] Hoftbagyi GN, Van Poznak C, Harker WG, Gradishar WJ, Chew H, Dahlkl 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):906–12.
[19] Van Poznak C, 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 : Off J Am Soc Clin Oncol 2017;35(35):3976–86.
[20] Groenvold M, Klee MC, Sprangers MA, Aaronson NK. Validation of the EORTC QLQ-C30 quality of life questionnaire through combined qualitative and quantitative assessment of patient-observer agreement. J Clin Epidemiol 1997;50(4):441–50.