Journal of Bone Oncology 5 (2016) 57–62

Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo

Review article

# Future directions for bone metastasis research – highlights from the 2015 bone and the Oncologist new updates conference (BONUS)

Ricardo Fernandes [a], Peter Siegel [b], Svetlana Komarova [b,c], John Hilton [a,d], Christina Addison [d], Mohammed F K Ibrahim [a], Joel Werier [d,e], Kristopher Dennis [f], Gurmit Singh [g], Eitan Amir [h], Virginia Jarvis [a], Urban Emmenegger [i], Sasha Mazzarello [d], Mark Clemons [a,d,*]

[a] Department of Medicine, Division of Medical Oncology, The Ottawa Hospital and University of Ottawa, Ottawa, Canada
[b] Department of Medicine, Goodman Cancer Research Centre, McGill University, Montreal, Canada
[c] Faculty of Dentistry, McGill University, Montreal, Canada
[d] Ottawa Hospital Research Institute and University of Ottawa, Ottawa, Ontario, Canada
[e] Department of Surgery, Division of Orthopaedic Surgery, The Ottawa Hospital and University of Ottawa, Ottawa, Canada
[f] Ottawa Hospital Division of Radiation Oncology and University of Ottawa, Ottawa, Ontario, Canada
[g] McMaster University, Hamilton, Canada
[h] Division of Medical Oncology, Department of Medicine, University Health Network and Princess Margaret Hospital and University of Toronto, Toronto, Canada
[i] Division of Medical Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada

ARTICLE INFO

*Article history:*
Received 30 November 2015
Received in revised form
10 February 2016
Accepted 10 February 2016
Available online 23 February 2016

*Keywords:*
Bone metastases
Cancer
Animal models
Cancer-induced pain

ABSTRACT

In an era of reduced peer-reviewed grant funding, performing academic bone oncology-related research has become increasingly challenging. Over the last 10 years we have held an annual meeting to bring together clinicians, clinician/scientists and basic biomedical researchers interested in the effects of cancer and its treatment on skeletal tissues. In the past these "*Bone and the Oncologist New Updates Conference (BONUS)*" meetings have served as critical catalyst for initiating productive research collaborations between attendees. The 2015 BONUS meeting format focused on potential key research themes that could form the basis of a coordinated national research strategy to tackle unmet clinical and research needs related to complications associated with cancer metastasis to bone. The three themes planned for discussion were: Is bone metastases-related pain the main issue facing patients? Are there new therapeutic targets for patients with bone metastases? How do we more firmly link basic science with clinical practice? We present a summary of lectures and commentaries from the attendees to serve as an example that other similarly motivated groups can model and share their experiences. It is our hope that these presentations will result in comments, feedback and suggestions from all those researchers interested in this important area.


## 1. Introduction

Over the last two decades, there has been a substantial increase in our understanding of the underlying biology of bone metastasis as well as the development and widespread incorporation of inhibitors of osteoclast function, namely bisphosphonates and denosumab, into clinical practice [1–3]. However, more recently there has been an international fall in peer-reviewed grant funding [4]. This trend is also clearly evident in the declining grant support provided by the three Canadian federal funding agencies (Canadian Institutes of Health Research (CIHR), Natural Sciences and Engineering Research Council of Canada (NSERC) and Social Sciences and Humanities Research Council (SSHRC) [4]. This has led to increased challenges in performing academic bone metastasis research. The "Bone and the Oncologist New Updates" (BONUS) meeting is an annual Canadian multidisciplinary conference on the interaction of bone and cancer biology [5,6]. The focus of the 2015 BONUS Conference (16 and 17 April 2015) was to discuss potential key research themes that could form the basis for a coordinated national research strategy to tackle unmet clinical and research needs related to complications associated with cancer metastasis to bone.

This article captures a two-day programme of multidisciplinary presentations, panel discussions and interactive dialogue on planning

* Corresponding author at: Division of Medical Oncology, The Ottawa Hospital Cancer Centre, 501 Smyth Road, Ottawa, Canada.
*E-mail address:* mclemons@toh.on.ca (M. Clemons).

http://dx.doi.org/10.1016/j.jbo.2016.02.004
2212-1374/

**Table 1**
Some unmet clinical and basic science questions.

| Basic Science | Clinical |
|---|---|
| Are osteoclasts the only stromal cell type that should be targeted therapeutically? | What are the major issues affecting cancer patients with bone metastasis? |
| Are there new cancer/bone-stromal targets that should be developed? | What do patients, nurses and clinicians feel are the most immediate concerns (bone pain, mobility issues, and survival)? |
| What is our understanding of the biological mechanisms of pain associated with bone metastasis? | Why do bisphosphonates and denosumab for metastatic bone cancers fail to prolong overall survival? |

a national strategy for bone metastasis research. We aimed to review the data on bone pain management, expand our capacity to address current and future development challenges, place strategies in the context of the widespread use of bone-targeting agents and to act as a forum for feedback and comments from other researchers interested in this field.

### *1.1. Preliminary discussions leading to BONUS 2015*

Prior to the BONUS 2015 meeting a preliminary meeting was held in Montreal in November of 2014. The “working group” felt that the development of specific research questions focused on “bone metastasis” should be formulated from the starting point of unmet clinical needs. In particular, the following issues were felt to be of key importance: Understanding the biology associated with the process of bone metastasis initiation and progression and developing potential treatment strategies to improve outcome of patients with bone metastases. Several questions were discussed that are outlined in Table 1. There was also a strong feeling that research initiatives should incorporate questions that cut across the cancer care continuum from basic biomedical research to clinical translation and patient outcomes. Based on the priorities discussed during the preliminary meeting, the following themes were selected for in-depth discussion at the 2015 BONUS meeting: Is bone metastases-related pain the main issue facing patients? Are there new therapeutic targets for patients with bone metastases? How do we more firmly link basic science with clinical practice? Each of these themes will be summarised below.

**Theme 1.** : Is bone metastases-related pain the main issue facing patients?

This session consisted of presentations about metastasis-related bone pain from the perspectives of patient experience and clinical care.

> “What are the current limitations of bone-targeted agents in relation to bone pain in patients with bone metastases?” Eitan Amir, MD

While any malignancy may metastasise to bone, it is most prevalent in advanced breast (70–80%), prostate (70–80%), thyroid (60%), lung (10–50%) and renal cancers (30%) [7–11]. The consequences of bone metastases include reduced survival, morbidity and pain that negatively affect the patient's quality of life (QoL) as well as skeletal-related events (SREs) [11,12]. Despite the fact that randomized trials of bisphosphonates, and denosumab, have shown reduced incidence of SREs, prolonged time to occurrence of SREs and an improvement in pain control, clear improvements in overall Quality of Life (QoL) have not been realized with their use. Two trials comparing pamidronate to placebo showed that patients in the pamidronate arms experienced less pain; however, there was no difference in the overall QoL [13]. Similarly, in the randomized trial comparing denosumab to zoledronic acid, improvements in QoL were observed in both arms with denosumab not showing consistently greater magnitude of improvement over the entire trial period. Whether QoL improvements resulted from the administration of bone targeted therapy or the concurrent administration of systemic anti-cancer therapy is unclear especially as the placebo-controlled randomized trials of bisphosphonates did not show differences in QoL between arms [13–14] Given that bone-targeting agents have not been found to affect overall or progression-free survival and have known risks and adverse effects, including rare but severe toxicities such as hypocalcaemia and osteonecrosis of the jaw (ONJ) [15–17], this lack of improvement in QoL is disappointing. As we have likely reached the limits of therapeutic osteoclast inhibition with bisphosphonates and denosumab there is increasing interest in the effects of other anti-cancer agents on the bone. For example, the use of new treatments for prostate cancer such as abiraterone acetate, enzalutamide and radium 223 have all shown decreased rates of SREs as well as improvements in survival. As a result, there is a need to develop better agents not only to reduce bone pain but to also identify strategies to optimise the use of bone-targeted agents as SREs become less common. As more effective cancer treatments become available, it will be important to further explore optimal dosing of bone-targeting agents in these patients.

> “What do patients with bone metastases need?” Virginia Jarvis, RN

Virginia Jarvis, a nurse specialist in pain and palliative care, followed up with a discussion of known as well as poorly understood needs of patients with bone metastases in ambulatory and palliative care. Pain assessment for patients with bone metastasis presents unique problems as pain is often incidental in nature with high pain scores with movement and minimal to zero pain scores at rest making the standard 0–10 verbal scoring system an ineffective tool. The Brief Pain Inventory was discussed as a pain assessment instrument that could best inform health care professionals to the actual pain state and help guide the clinician to the choice of appropriate treatments that may include interventional therapies that go beyond the World Health Organisation Analgesic Ladder. Indeed, in a large recently presented study, risk of SREs was correlated with worsening pain scores on the Brief Pain Inventory [19]. The unmet needs of patients include treatments such as physiotherapy, occupational therapy and social work as pain effects mobility, activities of daily living, the ability to drive and financial decline. Following this presentation there was extensive discussion around whether bone pain was the major issue facing patients or reduced mobility. This could be an important direction for future studies and requires further evaluation.

> “What are orthopaedic surgeons doing in 2015 for patients with painful bone metastases?” Joel Werier, MD

Orthopaedic stabilisation of osseous metastatic lesions can provide rapid and effective pain relief in patients presenting with significant bone destruction and impending or pathologic fracture. It is essential to develop a collaborative relationship between engaged orthopaedic surgeons and medical as well as radiation oncologists in order to facilitate multidisciplinary care of an individual patient. A clear understanding of life expectancy, patient expectations, and tumour biology

can help guide clinical and surgical decision making. For example, orthopaedic interventions could be significantly altered if it was evident that a patient had a very short prognosis. Tools to accurately evaluate patient prognosis in this setting could be invaluable. Minimally invasive techniques such as radiofrequency ablation, percutaneous cryoplasty, cementoplasty, and vertebroplasty can be effective in patients who are poor surgical candidates or who have a specific lesion that can be addressed by these techniques. Surgical stabilization is almost always supplemented with radiation to minimise tumour progression and implant failure. A collaborative approach with orthopaedic surgical consideration can greatly aid in the palliation, mobilisation, and quality of life of affected individuals. Basic and translational researchers should be invited to collaborate with clinicians caring for patients with metastatic bone disease. For example – is local delivery of biologics, incorportated into scaffods/cements used to stabilise surgical defects a useful approach? In addition, in our centre orthopaedic stabilization with tumour de-bulking is a unique opportunity to provide good quality tumour specimens for basic science and translational research investigating novel therapies.

"Study endpoints in trials of bone-targeted agents and radiotherapy – should bone pain be a criteria?" Kris Denis MD and Mark Clemons, MD

Traditionally, bisphosphonates have been evaluated in terms of SRE prevention; however, its definition has changed with time. For example, while older studies included hypercalcaemia as an SRE, most subsequent trials do not take it into account. Second, clinical trials often mandate bone surveys and isotope bone scans every 3 months, resulting in the detection of asymptomatic SREs. Including these asymptomatic events as endpoints makes it challenging to determine whether newer agents actually represent an improvement in preventing what truly matters to patients: symptomatic SREs [20–22]. Another factor limiting the use of SREs as a meaningful endpoint is that bone pain per se is not considered a SRE despite the fact that clearly impacts patient QoL and is tied to the use of radiotherapy. Indeed, the conditions under which radiotherapy has been indicated (and recorded as a SRE in previous trials) are not standardized. Indeed, a review of literature and survey on QoL perception outcomes of radiation therapy for bone metastasis has shown that the impact of metastatic disease and radiotherapy extends beyond pain [23]. Looking beyond simple endpoint metrics, perhaps an alternative way to measure the impact of bone metastases on patients is through a broader examination of QoL impact. The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group Bone Metastases Module (EORTC QLQ BM22) is a bone metastases-specific instrument that measures the impact of bone metastases on patients' quality of life. It has been extensively validated internationally and is well-suited to use within clinical trials [24].

*Conclusion 1:* Given that pain/mobility remains a significant issue for many patients, the group felt the first priority for future studies should be to investigate the experience in patients with bone metastatic cancer with regard to pain, mobility, fatigue, psychological distress, reduced performance and treatment side-effects. It will only be possible study the impact of all these issues in the individual patient with a dedicated bone metastasis health-related QoL tool.

**Theme 2.** Are there new targets for patients with bone metastases?

The second session involved presentations discussing the strategies and ideas in development of new treatment strategies for patients with bone metastases.

"Better use of established agents?" mark Clemons, MD

One of the ways to improve therapeutic outcomes would be to use current agents more effectively [25–26]. Given that patients with bone-only metastatic disease may experience longer term survival, and the risk of adverse events from bone-targeting agents increases with cumulative exposure, the question around optimal dose and dosing interval remains unanswered [26–28]. A survey of physicians who treat patients with bone metastases from breast cancer and metastatic castration-resistant prostate cancer showed significant variability in the use of bone-targeting agents, including the choice and dosing interval [29]. A systematic review evaluating de-escalated treatment (i.e. every 12 weeks) of breast cancer patients with bone-targeted agents in comparison to current standard practice of every 3–4 weeks showed a clear knowledge gap with regard to establishing the clinical benefits of de-escalated bone targeted agent therapy in metastatic breast cancer patients [24]. Similarly, a recent systematic review also demonstrated that denosumab 12-weekly was as effective as 4-weekly dosing in patients with bone metastases from prostate cancer ("in press"). Integration of these reduced frequencies of bone-targeted agents into routine clinical practice could benefit both patients (reduced visits to the cancer centre for treatment and less drug toxicity) and the health care system (lower drug costs).

For many years it has been hoped that use of biochemical endpoints, such as bone resorption markers, may offer a solution to the challenge of using pain scores by offering a quantitative, rather than qualitative, assessment of bone-targeting agent effect on the bone in the presence of skeletal metastases. Retrospective analyses of bisphosphonate trials suggest that early normalisation (at 3 months) of urinary N-terminal telopeptide levels in patients undergoing treatment with bisphosphonates are associated with a significantly reduced risk of a first SRE, first fracture, surgery to bone, or death [30]. However, incorporation of these biomarkers of bone turnover, pain scores and SREs to develop practical strategies to improve the care of patients has to date been extremely challenging [31–33].

"Models for bone metastases" Christina Addison, PhD

There are a number of pre-clinical animal models to study cancer metastasis to bone. Typically, approaches are employed that include syngeneic, transgenic and xenograft models of bone metastasis. Experimentally, the most frequent route of injection of cancer cells is intracardiac (into left cardiac ventricle), which permits seeding and colonisation of tumour cells in metaphyses of the long bones. Intratibial (intraosseous) injection of tumour cells directly into the marrow space is often used to examine tumour stromal interactions during the growth of bone metastatic lesions. Finally, vossicle models are emerging in which foetal human bone is implanted subcutaneously into mice, followed by intra-cardiac or local injection of human tumour cells that colonise the human bone fragments and form metastases. Histological and immunhistochemical techniques are employed to study excised tissues while increasingly, in vivo imaging modalities (optical imaging systems (IVIS), radiography, μCT and MRI) have been used to assess the growth of bone metastatic lesions and the effect on bone resorption/destruction.

While these models have been very useful in delineating mechanisms that drive the colonisation and growth of cancer cells in bone, they have not been interrogated sufficiently [33]. Hopefully these models can be utilised further to identify novel therapeutic targets and develop more effective treatment combinations that could enhance overall survival.

"New targets" john Hilton, MD

A series of potential emerging agents may be helpful in addressing bone-only disease. Cabozantinib (XL184) is an orally bioavailable tyrosine kinase inhibitor with potent activity against

MET and VEGFR2. In early clinical studies in patients with metastatic prostate cancer, cabozantinib demonstrated significant and rapid effects on bone scan lesions as well as on markers of bone formation and resorption, bone pain and narcotic use. In addition, statistically significant improvement in progression-free survival was seen with cabozantinib compared with placebo. While the subsequent larger registration study was negative in terms of overall survival, it again showed important findings in metastatic bone disease, including resolutions of metastases in bone scans and reductions in bone turnover markers [34]. It is possible that the observed clinical effects on bone are related to decreased RANKL expression in osteoblastic cells and inhibition of osteoclastogenesis and PTHrP-stimulated bone resorption, thus providing a rationale for beneficial skeletal observations while failing to control progression of the malignancy. It is also possible that cabozantinib should not be considered a bone-targeting agent per se, but as an effective anti-tumour agent given its efficacy in metastatic renal cell cancer [35]. Given the effects of cabozantinib on bone metastases in patients with castration resistant prostate cancer it would be interesting to see whether or not combinations with bisphosphonates or denosumab are synergistic or not.

"Radium 223 as a novel therapeutic for bone metastases" Urban Emmenegger, MD

Radium 223 is a "calcium mimetic" alpha emitter that selectively binds to areas of increased bone turnover such as bone metastases. In patients with castration-resistant prostate cancer, radium 223 significantly improved overall survival as well as time to first symptomatic skeletal related event [36]. QoL was also seen to be better with radium 223 versus placebo. Since radium 223 is the first bone-targeted agent with documented positive impact on overall survival. As with cabozantinib, mentioned above, it is also possible that as radium 223 delivers radiation to the bone metastases itself it should also be considered an anticancer agent and not just a bone-targeted agent. Results in other tumour types such as breast cancer are eagerly awaited.

"Immune therapies for bone metastases" Guy Ungerechts, Md

Targeted infection of cancer using novel oncolytic viral therapies via binding of tumour-specific surface receptors is an exciting and promising field. Therapy combining oncolytic virus with an immune checkpoint blockade for immunovirotherapy can lead to an immunomodulation and ultimately disease response. While immunomodulation may prove to be extremely important for effective tumour control in the bone microenvironment, tumour-specific receptors for bone metastatic lesions remain less well characterized.

**Theme 2 conclusion. :** Despite over two decades of widespread use of osteoclast-targeting agents such as bisphosphonates and more recently denosumab these have had no discernible effect on response rates, progression free or overall survival. Studies on dosing intervals with osteoclast-targeting agents continue to show that treatment can be safely de-escalated and studies are needed to explore their role in the presence of increasingly effective anticancer agents. However, clearly new targets are needed. Studies will need to integrate basic science models into clinical practice so that novel agents and their combinations can be more rapidly evaluated in the laboratory before performing large, expensive studies in patients.

**Theme 3.** How do we more firmly link basic science with clinical practice?

It is evident that there has to be meaningful collaboration between basic science and clinical practice. In the final session, bone metastasis models and their limitations were discussed. Finally, clinicians presented information on future directions in the bone metastasis research field. It was hoped that this would provide additional information for basic science collaboration.

"Animal models for bone cancer-induced pain" Svetlana V. Komarova, PhD

One of the factors limiting research into the area of bone cancer-induced pain is the limited number of animal models where treatment hypotheses can be tested. Dr Komarova presented data on the behavioural pain phenotype in an experimental breast cancer bone metastasis model and on the pain-relieving effects of microenvironment-targeting adjuvant therapies. In a mouse model, where immunocompetent mice were injected intra-tibialy with murine mammary carcinoma cells or saline, breast cancer bone metastasis was associated with gradual development of osteolysis, spontaneous limping and guarding of affected limbs, as well as a significant increase in the sensitivity to mechanical, heat and cold stimuli [37]. Moreover, unilateral breast cancer bone metastasis was found to drive hypersensitivity, bone remodelling and sensory neuronal plasticity at sites distant from the tumour area [38]. The anti-inflammatory and osteolysis-targeting drug rapamycin reduced hypersensitivity to mechanical and thermal stimuli in the cancer-bearing and contralateral limbs, while the osteoclast-targeting drug pamidronate reduced thermal sensitivity at the cancer-bearing and contralateral limbs. Thus, localised bone cancer drives osteolysis, sensory hypersensitivity, and neuroplasticity both locally and distantly from the primary lesion. Ultimately mechanistic based therapeutics is essential to develop novel agents for cancer induced bone pain.

Unfortunately, despite the promise of these models, there are difficulties in translating these studies to patient experience. First, while pain assessment in patients is generally done using validated questionnaires, such tools are not practical in animal studies. In contrast, quantitative sensory tests which assess the sensitivity thresholds to mechanical and thermal stimuli can be used in humans and animals, and were shown to be informative and predictive in patients with neuropathic and musculoskeletal pain [39–40], as well as chemotherapy-related pain in cancer patients [41–42]. However, the validity of quantitative sensory tests in providing measurable pain information in bone metastasis patients has been only assessed in a small number of patients [43], making it impossible to translate pain-related conclusions obtained in animal studies to patient care. In addition, the treatment protocol in experimental animals commonly does not reflect the usual treatment protocol in patients such as use of clinically relevant chemotherapy dosing schedules and time delay between initiation of bone metastasis and development of symptoms which will lead to treatment in patients. Thus, development of direct correlates between measures used to quantify the disease progression in animal models and in patients will help in knowledge translation from basic science studies to clinical care.

"Challenges of ex-vivo models for identifying new targets" Christina Addison, PhD

A significant limitation of the use of cell lines in breast cancer bone metastasis related research has been the fact that so many cell lines are from hormone receptor negative lines, when the vast majority of patients have hormone receptor positive disease. Dr. Addison and her team have therefore established a programme in collaboration with orthopaedic surgeons to obtain tumour tissue straight from the operative room from patients undergoing surgery for bone metastases complications. As a result, it is possible to isolate new bone metastatic-derived cancer cell lines, to test drug combinations in ex vivo bone metastatic tumour tissues and to develop patient derived xenograft models. There remain challenges in translating these

models into the clinical practice, such as a need to improve quantitative assays for tumour burden and ultimately evaluate response to treatment in vivo and models that can better mimic to the human in vivo phenotype.

"Bisphosphonates as adjuvant therapy for breast cancer and the relevance of the low estrogen environment" Alexander Paterson, MD

Since bisphosphonates were found to benefit patients with bone metastases from breast cancer, trials of adjuvant bisphosphonates in operable primary breast cancer were set up in the 1990s and early 2000s, some using end-points appropriate for a class of drugs whose dominant mode of action is in bone (e.g. bone metastasis-free interval and overall survival [OS]), and others, using traditional cancer trial endpoints (disease-free survival [DFS] and OS). Prior to these trials there was substantial pre-clinical and clinical evidence that bisphosphonates had anti-osteoclastic actions and there was some limited pre-clinical evidence of direct cytotoxic anti-tumour effects [33]. Importantly, there was also evidence in preclinical in-vitro and animal studies of the role of the "vicious cycle" in promoting bone metastasis growth [44–45]; and it was known that tumour growth could be inhibited using bisphosphonates [46].

Not surprisingly, DFS benefits have been difficult to demonstrate in any single trial (except ABCSG-12). Adjuvant clinical trials accrued breast cancer patients of all ages and these trials have not demonstrated clear benefits in the primary endpoints of DFS and OS. However, protocol stipulated analysis by stratification arms in the three largest randomized trials (post- and pre-menopausal in AZURE; or age $>50$ versus $<50$ in NSABP and Royal Marsden trials) revealed a significant benefit for DFS/OS in post-menopausal women (AZURE) and for bone metastasis-free interval and OS in women $>50$ (NSABP and Royal Marsden). Many clinical scientists believe that a consistent observation like this across three large, well-conducted independent trials is a powerful observation. Furthermore, using traditional chemotherapy primary end-points such as DFS (which includes second primaries, contra-lateral breast cancer and loco-regional recurrences) for assessing a bone drug is likely to miss a valuable clinical effect.

An individual patient-level meta-analysis of all adjuvant bisphosphonate trials was proposed by the EBCTCG and this study has now been published confirming the validity of the observation that bone-metastasis free survival and overall survival benefits occur in post-menopausal and older women receiving bisphosphonate therapy (either oral clodronate or intravenous aminobisphosphonates) [45]. The reason for this benefit is not clear. Suggestions have been proposed around the role of a "low estrogen environment". Interactions between reproductive hormones, tumour and bone cell biology, and marrow stem cells evolve during the menopausal transition where estradiol and inhibin dominate in the pre-menopausal woman, and activin and the TGF-beta superfamily dominate as bone metabolism regulators in the post-menopausal woman [46].

## 2. Conclusion

Bone oncology requires a multi-disciplinary team approach and a diverse arsenal of cancer therapeutics. The BONUS 2015 meeting was structured to identify unanswered research questions and unmet clinical needs that could form the basis for an integrated team grant application, with the goal of positively impacting the care of bone metastatic patients. This review summarizes the bone oncology-related topics presented and discussed among the meeting attendees. It is clear that many unsolved challenges and knowledge gaps currently exist that are barriers to effective treatment of metastatic bone disease, which represent opportunities for additional research by a multi-disciplinary team.

## Acknowledgements

The BONUS meeting received an funding from Amgen Canada. This funding was used to organise the meeting. No speaker was paid. The sponsor has had no role in the preparation of this manuscript.

## References

[1] M. Clemons, K.A. Gelmon, K.I. Pritchard, A.H.G. Paterson, Bone-targeted agents and skeletal-related events in breast cancer patients with bone metastases: the state of the art, Curr. Oncol. 19 (5) (2012) 259–268.
[2] N. Bouganim, G. Dranitsaris, E. Amir, M. Clemons, Optimising the use of bone-targeted agents in patients with metastatic cancers: a practical guide for medical oncologists, Breast Cancer Res. Treat. 146 (1) (2014) 153–162.
[3] C.M. Bouganim N1, Bone-targeted agents in the treatment of bone metastases: RANK outsider or new kid on the block, Futur. Oncol. 7 (3) (2011) 381–383.
[4] Federal Funding of Basic Research. Nature, 2012, 487, pp. 271–272.
[5] I. Kuchuk, D. Simos, C.L. Addison, M. Clemons, A national portfolio of bone oncology trials—The Canadian experience in 2012, J. Bone Oncol. 1 (2012) 95–100.
[6] X. Zhu, E. Amir, G. Singh, M. Clemons, C. Addison, Bone-targeted therapy for metastatic breast cancer—Where do we go from here? A commentary from the BONUS 8 meeting, J. Bone Oncol. 3 (2014) 1–4.
[7] R.E. Coleman, Metastatic bone disease: clinical features, pathophysiology and treatment strategies, Cancer Treat. Rev. 27 (3) (2015) 165–176, Available from ⟨http://www.sciencedirect.com/science/article/pii/S030573720090210X⟩.
[8] M. Kuchuk, C.L. Addison, M. Clemons, I. Kuchuk, P. Wheatley-Price, Incidence and consequences of bone metastases in lung cancer patients, J. Bone Oncol. 2 (1) (2013) 22–29 ⟨http://www.sciencedirect.com/science/article/pii/S2212137413000031⟩.
[9] R.J. Motzer, T.E. Hutson, P. Tomczak, M. Dror, R.M. Michaelson, O. Bukowski. Rixe. Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma. n engl j med Klin Onkol Oddzial Chemioterapii, Pozn Pol. PT Clevel Clin Found Clevel. RMB. 2007; 3562.
[10] A.T. Berman, A.D. Thukral, W.-T. Hwang, L.J. Solin, N. Vapiwala, Incidence and patterns of distant metastases for patients with early-stage breast cancer after breast conservation treatment, Clin. Breast Cancer 13 (2) (2015) 88–94, Available from ⟨http://www.sciencedirect.com/science/article/pii/S152682091200256X⟩.
[11] I. Kuchuk, B. Hutton, P. Moretto, T. Ng, C.L. Addison, M. Clemons, Incidence, consequences and treatment of bone metastases in breast cancer patients—Experience from a single cancer centre, J. Bone Oncol. 2 (4) (2015) 137–144, Available from ⟨http://www.sciencedirect.com/science/article/pii/S2212137413000560⟩.
[12] K. Harris, E. Chow, L. Zhang, G. Velikova, A. Bezjak, J. Wu, Patients' and health care professionals' evaluation of health-related quality of life issues in bone metastases, Eur. J. Cancer 45 (14) (2009) 2510–2518, Available from: ⟨http://www.sciencedirect.com/science/article/pii/S0959804909003815⟩.
[13] A. Lipton, R.L. Theriault, G.N. Hortobagyi, J. Simeone, R.D. Knight, K. Mellars. Pamidronate Prevents Skeletal Complications and Is Effective Palliative Treatment in Women with Breast Carcinoma and Osteolytic Bone Metastases Long Term Follow-Up of Two Randomized, Placebo-Controlled Trials.
[14] L.S. Rosen, D. Gordon, S. Tchekmedyian, R. Yanagihara, V. Hirsh, M. Krzakowski, et al., Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial–the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group, J Clin. Oncol. 21 (16) (2003) 3150–3157.
[15] A.T. Stopeck, A. Lipton, J.-J. Body, G.G. Steger, K. Tonkin, R.H. de Boer, et al., Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study, J Clin. Oncol. 28 (2010) 5132–5139, Available from: ⟨ ⟨www.jco.org⟩.
[16] K. Fizazi, M. Carducci, M. Smith, R. Damião, J. Brown, L. Karsh, Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study, Lancet 377 (9768) (2011) 813–822, Available from: ⟨http://www.sciencedirect.com/science/article/pii/S0140673610623446⟩.
[17] J. Shannon, J. Shannon, S. Modelevsky, A.A. Grippo, Bisphosphonates and osteonecrosis of the jaw, J. Am. Geriatr. Soc. 59 (12) (2011) 2350.
[19] R. von Moos, J.J. Body, B. Egerdie, A. Stopeck, J. Brown, L. Fallowfield, et al., Pain and analgesic use associated with skeletal-related events in patients with advanced cancer and bone metastases, Support. Care Cancer 24 (3) (2016) 1327–1337.
[20] K. Fizazi, A. Lipton, X. Mariette, J.-J. Body, Y. Rahim, J.R. Gralow, et al., Randomized phase ii trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous

bisphosphonates., J. Clin. Oncol. 27 (2008) 1564–1571, Available from: ⟨⟨www.jco.org⟩⟩.
[21] M.R. Smith, R.E. Coleman, L. Klotz, K. Pittman, P. Milecki, S. Ng, et al., Denosumab for the prevention of skeletal complications in metastatic castration-resistant prostate cancer: comparison of skeletal-related events and symptomatic skeletal events, Ann. Oncol. 6 (2004) 368–374.
[22] E. Chow, J. Nguyen, L. Zhang, L.-M. Tseng, M.-F. Hou, A. Fairchild, et al., International field testing of the reliability and validity of the EORTC QLQ-BM22 module to assess health-related quality of life in patients with bone metastases, Cancer. 118 (5) (2012) 1457–1465.
[23] M.F.K. Ibrahim, S. Mazzarello, R. Shorr, L. Vandermeer, C. Jacobs, J. Hilton, et al., Should de-escalation of bone-targeting agents be standard of care for patients with bone metastases from breast cancer? A systematic review and meta-analysis, Ann. Oncol. 26 (11) (2015) 2205–2213.
[24] C. Jacobs, et al., Pharmacotherapy of bone metastases in breast cancer patients–an update, Expert. Opin. Pharmacother. 15 (8) (2014) 1109–1118.
[25] D. Simos, C.L. Addison, I. Kuchuk, B. Hutton, S.C.M. Mazzarello, Bone-targeted agents for the management of breast cancer patients with bone metastases, J. Clin. Med. 2 (3) (2013) 67–88.
[26] I. Kuchuk, M. Clemons, C. Addison, Time to put an end to the “one size fits all” approach to bisphosphonate use in patients with metastatic breast cancer? Curr. Oncol. 19 (5) (2012) e303–e304, Available from: ⟨http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3457880&tool=pmcentrez&rendertype=abstract⟩.
[27] B. Hutton, C. Addison, S. Mazzarello, A.A. Joy, N. Bouganim, D. Fergusson, De-escalated administration of bone-targeted agents in patients with breast and prostate cancer—A survey of Canadian oncologists, J. Bone Oncol. 2 (2) (2013) 77–83, Available from: ⟨http://www.sciencedirect.com/science/article/pii/S2212137413000195⟩.
[28] C. Simmons, R.J. Broom, D.E. Cole, G. Dranitsaris, M. Clemons, Urinary N-telopeptide is a rapid predictor of response to and palliative benefit from bisphosphonate therapy in patients with metastatic breast cancer, Support. Cancer Ther. 4 (4) (2007) 182–187.
[29] C.L. Addison, N. Bouganim, J. Hilton, L. Vandermeer, S. Dent, E. Amir, 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 Cancer Res. Treat. 144 (2014) 615–624.
[30] C.L. Addison, G.R. Pond, H. Zhao, S. Mazzarello, L. Vandermeer, R. Goldstein, et al., Effects of de-escalated bisphosphonate therapy on bone turnover biomarkers in breast cancer patients with bone metastases, Springerplus 3 (2014) 577.
[31] M.J. Clemons, B. Cochrane, G.R. Pond, N. Califaretti, S.K.L. Chia, R.A. Dent, et al., Randomised, phase II, placebo-controlled, trial of fulvestrant plus vandetanib in postmenopausal women with bone only or bone predominant, hormone-receptor-positive metastatic breast cancer (MBC): the OCOG ZAMBONEY study, Breast Cancer Res. Treat. 146 (2014) 153–162.
[32] M. Clemons, K. Russell, L. Costa, C.L. Addison, Adjuvant bisphosphonate treatment forbreast cancer: why did something so elegant become so complicated? Breast Cancer Res. Treat. 134 (2) (2012) 453–457.
[33] R.J. Lee, P.J. Saylor, M.D. Michaelson, S.M. Rothenberg, M.E. Smas, D. T. Miyamoto, A dose-ranging study of cabozantinib in men with castration-resistant prostate cancer and bone metastases, Clin. Cancer Res. 19 (11) (2013) 3088–3094.
[34] C. Parker, S. Nilsson, D. Heinrich, O.'sullivan J.M. Helle SI, S.D. Fosså, et al., Alpha emitter Radium-223 and survival in metastatic prostate cancer, N Engl. J. Med. 3693369 (18) (2013) 213–223.
[35] D.M. Abdelaziz, L.S. Stone, S.V. Komarova, Osteolysis and pain due to experimental bone metastases are improved by treatment with rapamycin, Breast Cancer Res. Treat. 143 (2) (2014) 227–237.
[36] T.K. Choueiri, B. Escudier, T. Powles, P.N. Mainwaring, B.I. Rini, F. Donskov , H. Hammers, Cabozantinib versus everolimus in advanced renal-cell carcinoma, N Engl. J Med. 373 (19) (2015) 1814–1823.
[37] D.M. Abdelaziz, L.S. Stone, S.V. Komarova, Localized experimental bone metastasis drives osteolysis and sensory hypersensitivity at distant non-tumor bearing sites, Breast Cancer Res. Treat. 153 (1) (2015) 9–20.
[38] T.T. Baron R, Assessment and diagnosis of neuropathic pain, Curr. Opin. Support. Palliat. Care 2 (1) (2008) 1–8.
[39] R. Staud, E.E. Weyl, D.D. Price, M.E. Robinson, Mechanical and heat hyperalgesia highly predict clinical pain intensity in patients with chronic musculoskeletal pain syndromes, J. Pain. 13 (8) (2012) 725–735.
[40] (a) D.L. Hershman, L.H. Weimer, A. Wang, G. Kranwinkel, L. Brafman, D. Fuentes, et al., Association between patient reported outcomes and quantitative sensory tests for measuring long-term neurotoxicity in breast cancer survivors treated with adjuvant paclitaxel chemotherapy, Breast Cancer Res. Treat. 125 (3) (2011) 767–774;
(b) E.G. Vichaya, X.S. Wang, J.A. Boyette-Davis, T.R. Mendoza, Z. He, S. K. Thomas, et al., Subclinical pretreatment sensory deficits appear to predict the development of pain and numbness in patients with multiple myeloma undergoing chemotherapy, Cancer Chemother. Pharmacol. 71 (6) (2013) 1531–1540.
[41] A.C. Scott, S. McConnell, B. Laird, L. Colvin, M. Fallon, Quantitative sensory testing to assess the sensory characteristics of cancer-induced bone pain after radiotherapy and potential clinical biomarkers of response, Eur. J. Pain. 16 (2012) 123–133.
[42] G.R. Mundy, Metastasis to bone: causes, consequences and therapeutic opportunities, Nat. Rev. Cancer. 2 (8) (2002) 584–593.
[43] G.R. Mundy. Bone resorption and turnover in health and disease. Bone, 198, 8 Suppl 1, S9-16.
[44] K.N. Weilbaecher, T.A. Guise, L.K. Mccauley, Cancer to bone: a fatal attraction, Nat. Rev. Cancer 11 (6) (2011) 41–25.
[45] Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet [Internet]. 2015 Jul [cited 2015 Jul 24];386(10001):1353–61. Available from: ⟨http://linkinghub.elsevier.com/retrieve/pii/S0140673615609084⟩.
[46] K.M. Nicks, T.W. Fowler, N.S. Akel, D.S. Perrien, L.J. Suva, D. Gaddy, Bone turnover across the menopause transition The role of gonadal inhibins, Ann. N Y Acad. Sci. (2010) 153–160.