

██████████
National Institute for Health and Clinical Excellence
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15 July 2011

Dear ██████████,

Denosumab for the treatment of bone metastases from solid tumours

Breakthrough Breast Cancer is a pioneering charity dedicated to the prevention, treatment and ultimate eradication of breast cancer. We fight on three fronts: research, campaigning and education. Our aim is to bring together the best minds and rally the support of all those whose lives have been, or may one day be, affected by the disease. The result will save lives and change futures – by removing the fear of breast cancer for good.

This submission reflects the views of Breakthrough, based on our experience of working with people with personal experience of, or who are concerned about, breast cancer. We regularly consult with members of our Campaigns and Advocacy Network

(Breakthrough CAN) for their views on a range of breast cancer issues. Originally founded by women with personal experience of breast cancer, Breakthrough CAN brings together over 1,600 individuals, regional groups and national organisations to campaign for improvements in breast cancer research, treatments and services.

Through supporting and training members to become patient advocates in their own right, Breakthrough CAN aims to increase the influence of patients in decisions regarding breast cancer issues.

Breakthrough welcomes the opportunity to comment on the appraisal consultation document regarding the use of denosumab for the treatment of bone metastases from solid tumours.

Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the conditions)?

There is no cure for metastatic breast cancer – that is when cancer cells spread from the primary site, settle and grow at a new site in the body - so treatment options are used only to alleviate symptoms, delay progression or improve survival. If treatments can provide health benefits they may be able to allow patients to continue with normal daily activities such as caring for their families or simply enjoying spending quality time with their loved ones. For patients with metastatic breast cancer the importance of this cannot be

underestimated. It is therefore essential that as many treatment options as possible are made available to patients with metastatic breast cancer.

Bone is one of the most common sites for breast cancer metastasis and it is estimated up to 74% of advanced breast cancer patients will develop bone metastases.^{i,ii} These patients are at a high risk of developing skeletal related events (SREs), defined as pathological bone fractures, compression of the spinal cord or the need for palliative radiotherapy or major orthopaedic surgery for the treatment of bone metastasis.ⁱⁱⁱ SREs are a concern for patients with bone metastasis and can greatly affect quality of life causing disability, pain and hospitalisation. The primary goal for the treatment of bone metastases is to prevent the occurrence of SREs which are disruptive and uncomfortable to the patient and also costly to the NHS.

The current treatment for bone metastases and the prevention of SREs in advanced breast cancer patients is bisphosphonates such as zoledronic acid. This is administered by intravenous injection, every three to four weeks.

Some studies have compared denosumab with zoledronic acid in the treatment of bone metastases and the delay of SREs. In a randomised double blind trial Stopeck *et al*^{iv} found denosumab superior to zoledronic acid in delaying the first on-study SRE by 18% in advanced breast cancer patients with bone metastases (Hazard ratio (HR) 0.82). These patients also saw a delay in the time to multiple on-study SREs by 23% (HR 0.77). Overall survival, disease progression and rates of adverse events and serious adverse events were similar between groups. However, despite this, the observation that the onset of first and multiple on-study SREs could be delayed following treatment with denosumab shows this therapy has the potential to provide a better quality of life to patients affected by bone metastasis.

Similar results were found after an integrated analysis of the phase III denosumab versus zoledronic acid trial in patients with malignant bone lesions from breast cancer, prostate cancer, solid tumours and multiple myeloma.^v The median time to first on-study bone complication was 8.2 months longer in the patients treated with denosumab compared to those receiving zoledronic acid, demonstrating the ability of denosumab to delay first SRE. Furthermore, in a separate analysis of the Phase III trials researchers reported denosumab to be superior at delaying the worsening of pain of advanced cancer patients with bone metastases.^{vi}

Renal deterioration is the most significant toxicity associated with zoledronic acid and patients receiving this treatment can develop renal impairment or even renal failure.^{vii} As part of their treatment with zoledronic acid patient must undergo renal monitoring. Denosumab elimination is not reliant upon the body's renal function and so requires no renal monitoring. Denosumab can therefore offer an additional treatment option for groups of patients for whom zoledronic acid is not suitable, for example patients with renal failure or renal insufficiency, patients with bone metastases who are not receiving

intravenous therapy – denosumab is administered by subcutaneous injection - and patients being treated with platinum compounds.

Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Denosumab has been reported to have higher drug related and total costs compared to zoledronic acid.^{viii} However, whilst we recognise this elevated cost there are several health-related benefits that should be included in the QALY calculation.

Patients affected by SREs are more affected by chronic pain and fatigue than those without and this will usually lead to difficulties in leading a normal life. As discussed, denosumab has been reported to delay the worsening of pain in patients with bone metastases, indicating its benefit for these patients.^{vi} Furthermore, compared to denosumab, zoledronic acid was associated with a 2.7 fold increase in acute-phase reactions causing flu-like symptoms. These act as an added burden for patients who will then require additional monitoring and potential treatment, something that need not be considered for patients receiving denosumab.

Although denosumab does not offer overall survival benefits compared to zoledronic acid it can delay first and multiple SREs in advanced breast cancer patients with bone metastases.^{iv} Therefore, an additional benefit that should be considered is that of the cost of care incurred to the family and/or social services of incapacitated patients suffering from SREs. Additional considerations may include the costs of palliative therapies to manage and alleviate pain in patients affected by bone fractures including radiotherapy, the cost of travel to health centres and the difficulties for incapacitated patients to attend hospital appointments to get treatments. Advanced cancer patients consume a considerable amount of hospital resources as metastatic bone disease and subsequent SREs develop.^{ix} Therefore, delaying these events could potentially alleviate hospital burden. Taking this into consideration it may be possible that the savings on the overall costs associated with SREs could help compensate for the cost of denosumab.

As a organisation representing patients, Breakthrough would like to emphasise how crucial it is for breast cancer patients with bone metastases to have access to as many treatment options as possible, especially ones that can improve quality of life and allow as little disruption to normal life as possible.

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

The clinical trial data available comparing denosumab with zoledronic acid, whilst limited, does appear to be robust and includes three pivotal, double blinded trials. The trial comparing the two therapies for the treatment of bone

metastases in patients with advanced breast cancer contained 2,046 patients and was randomised.^{iv} When included in analysis with the other trials which compared the therapies in patients with prostate cancer and other solid tumours, a total of 5,700 patients were under consideration.^v As discussed, denosumab was found to be superior in delaying first and subsequent SREs.

If you require any further information please contact [REDACTED],
[REDACTED] on [REDACTED] or
[REDACTED]

Yours sincerely,

[REDACTED]
Breakthrough Breast Cancer

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ⁱⁱ Kozlow, W. and Guise, T.A. Breast cancer metastasis to bone: mechanisms of osteolysis and implications for therapy. *Journal of Mammary Gland Biology and Neoplasia*. 2005;10 (2):169–80.

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^v Lipton, A., Siena, S. Rader, M. *et al.* Comparison of denosumab versus zoledronic acid (ZA) for treatment of bone metastases in advanced cancer patients: An integrated analysis of 3 pivotal trials. Presented at the 35th European Society for Medical Oncology (ESMO) Congress, Milan, Italy, October 8-12, 2010. Abstract 1249P.

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^{ix} Pockett, R.D., Catellano, D., McEwan, P. *et al.* The hospital burden of disease associated with bone metastases and skeletal-related events in patients with breast cancer, lung cancer, or prostate cancer in Spain. *European Journal of Cancer Care* 2010;19(6):755-60.