Comments on the Denosumab ACD

1. **Prostate Cancer**

There appears to be a fundamental misunderstanding of the 2 separate clinical uses of bisphosphonates in prostate cancer namely prevention of skeletal related events and the treatment of bone pain.

Skeletal related events (SRE) are a composite endpoint invented by the pharmaceutical industry to show clinical significance of bisphosphonates (and other bone targeted agents such as denosumab) when the individual endpoints in their trials failed to show significance. For a critical analysis of this read the Cochrane review of bisphosphonate for prostate cancer published in 2006. The guideline group for CG58, of which I was clinical lead, reviewed all the data and were unconvinced. Many of the endpoints that make up SRE are of little clinical relevance. Hence the recommendation not to use bisphosphonates for the prevention of skeletal related events in prostate cancer.

Bisphosphates have also been shown to reduce pain from bone metastases. This is distinct from the prevention of bone pain which is one of the constituents of SRE. The evaluation report on denosumab confuses the prevention of pain that is part of SRE with the separate use of bisphosphonates for the treatment of established pain. In fact, the evaluation report does not appear to have reviewed any of the data on bisphosphonates for the treatment of pain (I am not even sure that there is any for denosumab). Again the CG58 guideline group reviewed the bisphosphonate evidence for pain relief and made a recommendation that bisphosphonates could be used for pain relief when other measures had failed. This has nothing to do with prevention of skeletal related events.

Therefore, I cannot see how the Denosumab ACD can make any recommendation for prostate cancer either for skeletal related events or for the treatment of bone pain.

2. **Breast Cancer**

I was not involved in the development of CG81 but the guideline group appears to have taken a much less sceptical view of bisphosphonates for the prevention of SRE than the prostate cancer guideline group.

Reading the evaluation report for denosumab it is clear from the denosumab versus best supportive care comparisons that the cost effectiveness of zoledronate is questionable. Unfortunately this technology appraisal decided not to cover the comparison of zoledronate with best supportive care. It is also disappointing that the only comparator was zoledronate which is one of the most expensive bisphosphonates. There are a number of less costly generic bisphosphonates and no evidence that one bisphosphonate is superior to another. This is why the recommendations in both CG58 and CG81 do not specify a particular bisphosphonate.

Using the data in the denosumab evaluation report one of the health economists at NCC-C has calculated that the ICERs for zoledronate versus best supportive care for the prevention of SREs in prostate cancer and breast cancer are £293,900 and £316,714 respectively. This not an issue for

prostate cancer because CG58 makes a do not use recommendation for zoledronate. For breast cancer it appears that denosumab is only cost effective when compared to a non-cost effective treatment.

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