NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Response to Appraisal Consultation Document II

Denosumab for the treatment of bone metastases from solid tumours

Amgen Limited

2/7/2012

Academic in confidence information is reacted: [redacted]

Summary

Thank you for the opportunity to respond to the second Appraisal Consultation Document (ACD II) for denosumab (issued May 31 2012).

We welcome the Institute's positive recommendation of denosumab for the prevention of skeletal-related events (SREs) in adults with bone metastases in patients with breast cancer and also in patients with other solid tumours. We are also pleased that the Appraisal Committee made amendments in response to comments on the first ACD made by Amgen (*ACD II: Section 4.3.8, page 31; Section 4.3.9, page 32; Section 1.3, page 3*).

However, and with respect, we do not agree with Appraisal Committee's decision to withdraw the positive recommendation for use of denosumab in prostate cancer on the grounds that zoledronic acid is not the suitable comparator in this patient group. Amgen believe that there are strong and compelling reasons, based on the Institute's methods guide on comparator selection, why zoledronic acid should be considered an appropriate comparator for prostate cancer patients with bone metastasis in this appraisal of denosumab for SRE prevention:

- Bisphosphonate use, and specifically zoledronic acid, for the prevention of skeletal-related events (SREs) in prostate cancer, is embedded in UK clinical practice, with clear evidence of use: Bisphosphonates are used in approximately half of all prostate cancer patients with bone metastasis in the UK, among which they are used more frequently as a treatment to prevent SREs (56% of patients) than they are for pain relief (42% of patients). Of prostate cancer patients receiving a bisphosphonate, 92% were given zoledronic acid.

- Zoledronic acid is the only bisphosphonate with demonstrated efficacy and a license for use in prostate cancer, and is specifically indicated for SRE prevention. The Clinical Guideline 58 (CG58) recommendation against the use of bisphosphonate to prevent or reduce the complications of bone metastases in prostate cancer was based on inappropriate conclusions, underestimating the efficacy of zoledronic acid. This is reflected by the continued use of zoledronic acid to prevent SREs in prostate cancer patients in UK clinical practice, despite the CG58 recommendation.

- Pain relief is implicitly part of the SRE prevention indication, since the SRE composite end point captures an intervention for the management of pain (i.e. radiation to the bone) and is therefore within the remit of this appraisal. Since CG58 recommends bisphosphonate use for pain relief in prostate cancer, zoledronic acid is an appropriate comparator.

Regardless of clinical intent (i.e. for the relief of pain or prevention of SREs), denosumab compared to zoledronic acid, shows improved efficacy in prevention of SREs (which includes radiotherapy to the bone for pain relief) in the relevant prostate cancer population recommended to receive bisphosphonates by CG58 (i.e. patients with painful bone metastasis for whom other treatments including analgesics and palliative radiotherapy have failed). The use of denosumab in this population, in the place of bisphosphonates, provides the NHS with a treatment option that is economically dominant, i.e. delivering improved outcomes for patients with cost savings to the NHS.

Our aim within Amgen has been to deliver high quality, robust, comparative clinical trial evidence in response to HTA requirements. To this end, we have conducted the largest and most robust clinical trial programme in patients with bone metastases from solid tumours to-date, and have demonstrated unequivocal clinical superiority and dominant cost-effectiveness for denosumab against zoledronic acid, the standard of care within the UK, across all solid tumours. Despite this, we feel that NICE have made a preliminary recommendation, which will deny prostate cancer patients with bone metastases access to denosumab, based on a technicality relating to the wording of treatment intent and resulting comparator selection, whilst ignoring current UK practice, head to head clinical evidence, and principles of evidence-based medicine.

Amgen believe that the preliminary recommendation for denosumab, which excludes prostate cancer patients based on a technicality in comparator selection, is perverse and will inevitably result in iniquitous access to treatment for patients with bone metastasis from advance solid tumours across the UK.

We kindly request that NICE reconsider its preliminary recommendation against the use of denosumab as a treatment option in prostate cancer patients with bone metastases, and revise the recommendation to allow for the use of denosumab where zoledronic acid is currently used for SRE prevention in prostate cancer in UK clinical practice, specifically:

Denosumab is recommended as an option for preventing skeletal-related events in adults with bone metastases from prostate cancer if:

-zoledronic acid would otherwise be prescribed for these patients *and*

-the manufacturer provides denosumab with the discount agreed in the patient access scheme.

1 UK bisphosphonate treatment patterns in prostate cancer

Bisphosphonate use and treatment Intent

Bisphosphonate use, and specifically zoledronic acid, for the prevention of skeletal-related events (SREs) in prostate cancer is embedded in UK clinical practice. It is therefore an appropriate comparator for the prevention of SREs in prostate cancer in this appraisal.

The Appraisal Committee concluded that *'because the intention of the guideline on prostate cancer (NICE clinical guideline 58) was to recommend bisphosphonates for pain relief, the appropriate comparator for patients with metastatic prostate cancer in an appraisal considering the prevention of skeletal-related events is best supportive care' (ACD II: Section 4.3.4, page 29).*

We would wish to remind the Committee of the Institute's own guidelines on comparator selection, namely; Section 2.2.4 of the Guide to Methods of Technology Appraisal (June 2008), where it states that "*Relevant comparators are identified, with consideration given specifically to routine and best practice in the NHS (including existing NICE guidance)'* and also in Section 2.2.4 where it states '*There will often be more than one relevant comparator technology because routine practice may vary across the NHS and because best alternative care may differ from routine NHS practice.'*

Despite the recommendations of CG58 for bisphosphonate use only for pain relief, it is clear that there is variation in clinical use of bisphosphonates in prostate cancer across the UK, as recognised by the Appraisal Committee (Section 4.3.4, page 28). This reflects the mixed view among prostate cancer treating physicians regarding the relative benefits of bisphosphonates for pain relief or SRE prevention in the management of bone metastases. A UK patient chart review of treatment patterns shows that bisphosphonates are routinely used in approximately half of all prostate cancer patients with bone metastasis in the UK, among which they are used more frequently as a treatment to prevent SREs (56% of patients) than they are for pain relief (42% of patients):

Table 1 presents the results from a UK patient chart review of 1161 prostate cancer patients with bone metastases (Kantar Health 2010[1]), showing bisphosphonate treatment rates and reasons for initiation. The review shows that in 68% of prostate cancer patients with bone metastases, bisphosphonates were prescribed (currently or previously treated) or planned for future use. Of those currently treated, 56% were given bisphosphonates to prevent SREs and 42% to treat/prevent pain. In addition, treatment patterns from the IMS Oncology Analyzer™[2] for patients prescribed bisphosphonates show that zoledronic acid is the most commonly used bisphosphonate in prostate cancer, used in 92% of patients who receive a bisphosphonate; reflecting that zoledronic acid is the only bisphosphonate with demonstrated efficacy and a license for use in prostate cancer.

Therefore we feel there is strong evidence demonstrating that zoledronic acid use for the prevention of SREs in patients with prostate cancer is embedded in UK clinical practice. This is backed up by clinical expert testimony, both within the assessment report *(TAR: Section 3.2.1, page 11),* and from the experts at the first Appraisal Committee meeting on 8th March 2012. As such, and in line with the Institute's own methods guide, both

bisphosphonates (zoledronic acid) and best supportive care are relevant comparators in prostate cancer in this appraisal.

Table 1. UK bisphosphonate treatment patterns in prostate cancer1

Bisphosphonate treatment rates	Prostate cancer patients with bone metastases
Currently or previously treated	49%
Not currently treated but treatment with a bisphosphonate is planned	19%
Will probably never treat	32%
Reasons for initiation of bisphosphonate treatment	Prostate cancer patients currently treated with bisphosphonates
Prevent SREs	56%
To treat/prevent pain	42%
To treat bone metastases/lesions at original site	27%
To prevent new bone metastases/lesions	21%
Patient's disease has high risk factors	18%
End of anti-tumour treatment	<1%
Other	3%

Prostate cancer patient population treated with bisphosphonates

Whilst there is some variation within the UK, regarding clinical intent of bisphosphonate use in prostate cancer, i.e. **why** patients are treated (for pain relief or SRE prevention), there is broad agreement on the patient population treated with bisphosphonates i.e. **who** receives treatment; with the appraisal committee recognising that in UK clinical practice, bisphosphonates are used in those patients as recommended by CG58 - *'The Committee heard from clinical specialists that where zoledronic acid is used, it is used in accordance with the guideline on prostate cancer (NICE clinical guideline 58) in people with hormone-refractory (castration resistant) prostate cancer with painful bone metastasis for whom other treatments including analgesics and palliative radiotherapy have failed' (ACD II: Section 4.3.4, page 28).*

Importantly, evidence from prostate cancer Study 103 has demonstrated improved efficacy for denosumab compared to zoledronic acid for prevention of SREs (which includes radiotherapy to the bone for pain relief), in a specific subgroup of patients (with a prior SRE) which aligns with those patients recommended to receive bisphosphonates by CG58 i.e. in painful bone metastasis for whom other treatments including analgesics and palliative radiotherapy have failed. Baseline characteristics of the prior SRE subgroup for Study 103 show that 80% of patients had pain at baseline and 75% had received radiotherapy to the bone prior to entry into the study.

The appraisal committee recognises that in UK clinical practice, bisphosphonates are used in those patients as recommended by CG58, i.e. for patients with painful bone metastases for whom other treatments including analgesics and palliative radiotherapy have failed. Importantly, evidence from prostate cancer Study 103 has demonstrated improved efficacy for denosumab compared to zoledronic acid for prevention of SREs (which includes radiotherapy to the bone for pain relief) in a specific subgroup of patients (with a prior SRE) which aligns with those patients recommended to receive bisphosphonates by CG58.

Inadequate consultation on clinical expert advice on bisphosphonate use

Amgen believe that, within this appraisal process, efforts to obtain a complete picture of bisphosphonate clinical intent for use and efficacy, from a broadly representative group of UK clinicians, were inadequate. The NICE consultation process resulted in unbalanced testimony, since those clinical experts invited by the Institute to be present at the first Appraisal Committee meeting were not invited to attend the second meeting, even though it was clear from the ACD consultation that the topic of clinical intent for bisphosphonate use would be discussed for the first time in this appraisal. Section 3.5.36 of the Institute's MTA process guides state that '*If clarification of issues raised during the consultation period is required, the Chair of the Appraisal Committee can, at their discretion, invite one or more of the clinical specialists, NHS commissioning experts or patient experts to attend* (the second Appraisal Committee meeting)*'*. Given the variation within the UK for bisphosphonate use in prostate cancer regarding clinical intent, Amgen would have welcomed the Chair of the Appraisal Committee exercising their discretion to allow broader clinical expert advice to be sought on the topic.

2 Efficacy of bisphosphonates in the prevention of SREs in prostate cancer patients

Zoledronic acid is the only bisphosphonate with demonstrated efficacy and a license for use in prostate cancer, and is specifically indicated for SRE prevention. The CG58 recommendation against the use of bisphosphonates to prevent or reduce the complications of bone metastases in prostate cancer was based on inappropriate conclusions of zoledronic acid efficacy.

Zoledronic acid is the only bisphosphonate with demonstrated efficacy and a license for use in prostate cancer, and is specifically indicated for SRE prevention. However, the appraisal committee states that *'The Committee understood that the* [CG58] *group considered evidence from a systematic review and meta-analysis and, based on that evidence, did not recommend bisphosphonates for preventing skeletal-related events in prostate cancer' (ACD II: Section 4.3.4, page 28).*

The CG58 recommendation was based on inappropriate conclusions on the efficacy of zoledronic acid in SRE prevention. The Cochrane review, which formed the basis of the evidence for assessment of efficacy for bisphosphonates in the prevention of SREs within CG58, conducted an inappropriate meta-analysis analysis which resulted in an underestimate of efficacy of zoledronic acid in SRE prevention in prostate cancer patients:

- The Cochrane analysis assumed a bisphosphonate class effect and inappropriately pooled data for different bisphosphonates from three RCTs of bisphosphonate versus placebo. However, only the zoledronic acid RCT (Saad 2002[3]) demonstrated statistically significant improvements in SRE prevention compared to placebo, and was the basis for approval for its licensed indication in SRE prevention. Neither of the RCTs evaluating disodium pamidronate (Small 2003[4]) or sodium clodronate (Dearnaley 2003[5]), showed evidence of efficacy in SRE prevention (with no significant differences from placebo) and

as a consequence neither are licensed for SRE prevention or pain relief in prostate cancer.

- The Cochrane analysis also included RCTs not relevant to SRE prevention: the study evaluating disodium pamidronate (Small 2003[4]) was primarily a pain control study and did not report sufficient detail on the SRE prevention outcomes, whilst the RCT evaluating sodium clodronate (Dearnaley 2003[5]) was a bone metastases prevention study and therefore was not in the appropriate population to assess SRE prevention.

The assessment of efficacy of bisphosphonates in SRE prevention should therefore have been conducted without assumption of a class effect and only including relevant SRE data. This was the approach taken within the current technology appraisal, in which both network meta-analyses (conducted by Amgen and the Assessment Group) included only the zoledronic acid RCT (Saad 2002[3]), whilst excluding the disodium pamidronate RCT and the sodium clodronate RCT for the reasons stated above. Both of these network meta-analyses showed a significant effect for zoledronic acid in SRE prevention in prostate cancer.

The Cochrane review, through its inappropriate use and pooling of data was therefore biased against zoledronic acid and underestimated the efficacy of zoledronic acid, leading to a recommendation against its use for SRE prevention by CG58.

3 Value of SRE prevention in patients with prostate cancer

Men with prostate cancer and bone metastases in the UK are in need of treatments for SRE prevention, which will become increasingly clinically meaningful to both patients and treating physicians because of improvements in patient survival.

Prostate cancer patients with bone metastases carry the burden of terminal disease; SREs (following bone metastases) can result in incapacitating clinical sequelae including pathological fractures, radiation to bone, spinal cord compression, or surgery to bone, which can significantly add to that burden. SREs can dramatically erode quality of life, and the pain associated with bone metastases and SREs is significant, debilitating and difficult to treat. The prevention or delay of SREs can therefore provide meaningful benefits to these patients.

Within the UK there were an estimated 38,151 prostate cancer patients with bone metastases in 2011. Evidence from a UK patient chart review shows that 79% of prostate cancer patients with bone metastases have a moderate to high risk of SREs and that 49% of patients have been, or are treated, with bisphosphonates[1]. Since publication of CG58 (2008), there have been a number of interventions licensed for the treatment of metastatic prostate cancer. It is reasonable to assume that these will result in improved survival among patients with metastatic prostate cancer in the UK (e.g. NICE TA259 positive recommendation for abiraterone[6]) and as a consequence, SRE prevention will become increasingly important and clinically meaningful to both prostate cancer patients and all treating clinicians.

4 Pain relief is implicitly part of the SRE prevention indication

Pain relief is implicitly part of the SRE prevention indication, since the SRE composite end point captures an intervention for management of pain (i.e. radiation to the bone) and is therefore within the remit of this appraisal. Since CG58 recommends bisphosphonate use for pain relief in prostate cancer, zoledronic acid is an appropriate comparator.

The CG58 evaluated bisphosphonates separately for pain relief and for the prevention or reduction of the complications of bone metastasis (i.e. SREs), and whilst they make a negative recommendation specifically for SRE prevention, they recommend bisphosphonates for pain relief in patients with painful bone metastases for whom other treatments including analgesics and palliative radiotherapy have failed. The Appraisal Committee however noted that '*neither denosumab nor any of the bisphosphonates has marketing authorisation for pain relief in this group and that pain relief on its own was not in this appraisal's remit' (ACD II: Section 4.3.4, page 28)*'.

However Amgen believes that this is an artificial distinction and that pain management is implicitly part of the SRE prevention and is therefore within the remit of this appraisal: The SRE composite end point captures an intervention for the management of pain (i.e. radiotherapy to the bone) and is an objective measure of worsening pain / pain progression, compared to patient reported outcomes that assess pain. Treatments that prevent radiotherapy to the bone have prevented worsening pain / pain progression and so have provided pain relief. Table 2 presents the distribution of first on-study SRE by type, for the prostate cancer Study 103, and shows that radiotherapy to the bone is the most commonly reported SRE in all patients with prostate cancer (52.3% of patients) and also in the subgroup of patients with a prior SRE (55.0% of patients). Therefore, by preventing SREs in this patient population, treatments are providing pain relief.

Table 2. Distribution of first on-study SRE by type of SRE in prostate cancer Study 103

	All patients[7]		**Prior SRE subgroup**[8]	
	Denosumab N = 950	Zoledronic Acid N = 951	Denosumab N = 232	Zoledronic Acid N = 231
Overall n (%)	341 (35.9)	386 (40.6)	[redacted]	[redacted]
Pathological fracture n (%*)	137 (40.2)	143 (37.0)	[redacted]	[redacted]
Radiation to bone n (%*)	177 (51.9)	203 (52.6)	[redacted]	[redacted]
Surgery to bone n (%*)	1 (0.3)	4 (1.0)	[redacted]	[redacted]
Spinal cord compression n (%*)	26 (7.6)	36 (9.3)	[redacted]	[redacted]
*% is based on the number of subjects with an SRE				

5 Clinical benefit and cost-effectiveness of denosumab over zoledronic acid in prostate cancer patients.

Regardless of clinical intent, denosumab is a more effective treatment than zoledronic acid and is cost saving in those prostate cancer patients recommended to receive bisphosphonates by CG58.

Regardless of clinical intent (for relief of pain or prevention of SREs), compared to zoledronic acid, denosumab shows improved efficacy in prevention of SREs, including pain relief, in prostate cancer patients.

Table 3 presents a summary of results from Study 103 in prostate cancer to show the efficacy of denosumab compared to zoledronic acid for the individual pain-related SRE component (prevention of radiation to the bone), for Patient Reported Outcome Measures (PROMs) of pain relief, as well as prevention of all SREs using the composite SRE endpoint.

The data show that in prostate cancer patients, denosumab has demonstrated improved efficacy over zoledronic acid in relieving pain, as assessed using time to first radiation to the bone (an intervention for the management of pain); significantly reducing the risk of first radiation to the bone by [redacted] in patients with prostate cancer (p = [redacted] adjusted p value). There was also a significant delay in median time to first radiation to the bone compared with zoledronic acid in patients with prostate cancer (not estimable versus [redacted] weeks for zoledronic acid).

Denosumab has also demonstrated improved efficacy over zoledronic acid in relieving pain, as assessed by PROMs; denosumab delayed the time to development of moderate or severe pain compared with zoledronic acid, in patients with no or mild pain at baseline (5.8 versus 4.9 months, p = 0.1416), decreased the proportion of patients who progressed to moderate or severe pain (a relative decrease of 13.7% over 73 weeks) and reduced the number of patients who progressed from low analgesic use to strong opioids (a relative decrease of 11.7% over 73 weeks).

Finally, denosumab has demonstrated superior efficacy over zoledronic acid in prevention of all SREs, as assessed using the composite SRE endpoint (which includes pathological fracture, radiotherapy to bone, surgery to bone or spinal cord compression); significantly reducing the risk of first on-study SRE by 18% in prostate cancer (p = 0.008, adjusted p value). There was also a significant delay in median time to first on-study SRE compared with zoledronic acid in patients with prostate cancer (20.7 versus 17.1 months, 3.6 month delay).

Table 3. Efficacy of denosumab in pain reduction/ prevention of SREs

	Denosumab (N = 950)	**Zoledronic Acid (N = 951)**
Individual pain-related SRE component[8]		
Time to first radiation to the bone n (%)	[redacted]	[redacted]
Median time, months[a]	[redacted]	[redacted]
HR[b] (95% CI)	[redacted]	
P value	[redacted]	
Patient reported outcome measures of pain		
Time to moderate or severe worst pain[a] (BPI score >4) [9]		
Patients with baseline worst pain score ≤4	521	524
Median time a, months[§]	5.8	4.9
HR (95% CI)	0.89 (0.77, 1.04)	
p value[b]	0.1416	
Proportion of patients who progress to moderate or severe pain after 73 weeks9	N=950	N=951
Relative decrease	13.7% over 73 weeks	
Proportion of patients who progressed from low analgesic use to strong opioids after 73 weeks9	N1=821	N1=810
Relative decrease	11.7% over 73 weeks	
Composite SRE endpoint[7]		
Time to first on-study SRE n (%)	341 (35.9)	386 (40.4)
Median time, months[a]	20.7	17.1
HR[b] (95% CI)	0.82 (0.71, 0.95)	
p value non-inferiority	0.0002	
p value superiority[c]	0.008	

[a]Kaplan-Meier estimate; [b] HR is the same for non-inferiority and superiority analysis, based on Cox proportional hazards model with treatment groups as the independent variable and stratified by study (for overall only) and the randomised stratification factors; [c] P values were adjusted for multiplicity using the Hochberg Procedure; [§]Converted from days using conversion factor of 30.4375, N, Number of patients randomised, N1, Number of subjects with baseline analgesic score ≤ 2

Importantly the results from the prostate cancer Study 103 show that denosumab provides superior efficacy to zoledronic acid in the prior SRE patient subgroup, which aligns with the patient population recommended by CG58 to receive bisphosphonate, i.e. in prostate cancer patients with painful bone metastasis for whom other treatments including analgesics and palliative radiotherapy have failed. Therefore denosumab is superior to zoledronic acid in preventing further radiotherapy to the bone (i.e. preventing pain interventions and so managing pain), in patients who have already experienced radiotherapy to the bone.

Denosumab provides consistent clinical benefits over zoledronic acid for pain relief in prostate cancer, using both the objective measure of a pain management intervention (radiation to the bone) and Patient Related Outcomes Measures, in addition to clinical superiority over zoledronic acid in the prevention of composite SREs.

Further, because denosumab has proven superior efficacy over zoledronic acid, this has been modelled by both Amgen and the Assessment Group to deliver superior overall health outcomes (in terms of QALYs gained) for denosumab compared to zoledronic acid, at a lower total cost. Therefore, regardless of the clinical intent for bisphosphonate use as recommended in NICE CG58, denosumab is a cost-effective alternative to zoledronic acid in prostate cancer patients with bone metastasis.

The use of denosumab in place of bisphosphonates, in those prostate cancer patients recommended to receive bisphosphonates by CG58, provides a treatment that is dominant i.e. delivering improved outcomes for patients with cost savings to the NHS.

6 Perverse recommendation

Denosumab has demonstrated, across three phase III RCTs, a superior, statistically significant, clinically meaningful, consistent and robust treatment effect for the reduction in the occurrence of SREs compared with zoledronic acid in breast, prostate and other solid tumours; also accompanied by clinically meaningful improvements in pain management compared to zoledronic acid. This clear clinical benefit of denosumab over the standard of care within the UK, combined with a patient access scheme offered by Amgen, has ensured that denosumab, in the relevant prostate cancer patient population (as defined by CG58) dominates the current standard of care; providing cost saving improved outcomes to the NHS.

Our aim within Amgen has been to deliver high quality, robust, comparative clinical trial evidence in response to HTA requirements. To this end we have conducted the largest and most robust clinical trial programme in patients with bone metastases from solid tumours to-date and have demonstrated unequivocal clinical superiority and dominant cost-effectiveness for denosumab against zoledronic acid, the standard of care within the UK. Despite this, NICE have made a preliminary recommendation, which denies prostate cancer patients with bone metastases access to denosumab based on a technicality relating to the wording of treatment intent and resulting comparator selection, whilst ignoring current UK practice, head to head clinical evidence, and principles of evidence-based medicine.

Amgen believe that the preliminary negative recommendation in prostate cancer is perverse and will inevitably result in iniquitous access to treatment for patients with advanced cancer across the UK.

Amgen kindly request that NICE reconsider its preliminary recommendation against the use of denosumab as a treatment option in prostate cancer patients with bone metastases, and revise the recommendation to allow for the use of denosumab where zoledronic acid is currently used for SRE prevention in prostate cancer in UK clinical practice, specifically:

Denosumab is recommended as an option for preventing skeletal-related events in adults with bone metastases from prostate cancer if:

-zoledronic acid would otherwise be prescribed for these patients *and*

-the manufacturer provides denosumab with the discount agreed in the patient access scheme

References

[1] Amgen. Data on file: Kantar Health – Patient Chart Review. 2010.

[2] Amgen. Data on file: IMS Oncology Analyzer.

[3] Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst.* Oct 2 2002;94(19):1458-1468.

[4] Small EJ, Smith MR, Seaman JJ, Petrone S, Kowalski MO. Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. *J Clin Oncol* 2003;21:4277-84.

[5] Dearnaley DP, Sydes MR, Mason MD, Stott M, Powell CS, Robinson AC et al. A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial). *Journal of the National Cancer Institute* 2003;**95**:1300-11.

[6] NICE technology appraisal guidance TA259: Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen. Issued June 2012. http://publications.nice.org.uk/abiraterone-for-castration-resistant-metastatic-prostate-cancer-previously-treated-with-a-ta259.

[7] Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet.* Mar 5 2011;377(9768):813-822.

[8] Amgen. Data on file: 20050103 (Study 103) Clinical Study Report, Abbreviated. 23 April 2010.

[9] Brown J. Pain outcomes in patients with bone metastases from castrate-resistant prostate cancer: results from a phase 3 trial of denosumab vs zoledronic acid. Paper presented at: European Association of Urology 2011.