National Institute for Health and Care Excellence

Denosumab for prolonging bone metastasis-free survival in castrate-resistant prostate cancer

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Amgen	No comments	Comment noted
	British Association of Urological Surgeons	Yes. This is a new technology and a new potential indication for that technology. The results of a recent large scale RCT testing the drug for the indication of reduction in the rate of development of new bone metastases showed a reduction in the time to development of new lesions. This is the first time that this has been shown by any agent in this condition.	Comment noted. No changes to the scope required.
	Royal college of pathologists	Yes appropriate	Comment noted. No changes to the scope required.
	Royal college of physicians	Yes	Comment noted. No changes to the scope required.
		Yes	Comment noted. No changes to the scope required.
Wording	Amgen	Amgen recommends the wording of the remit is redefined from hormone-refractory prostate cancer to castrate-resistant prostate cancer in accordance with the proposed indication for denosumab.	Comments noted. The wording of the draft remit has been amended accordingly.
	British Association of Urological Surgeons	Yes	Comment noted. No changes to the scope required.
	Royal college of pathologists	Yes	Comment noted. No changes to the scope required.

Section	Consultees	Comments	Action
	Royal college of physicians	Yes	Comment noted. No changes to the scope required.
Timing Issues	Amgen	No comments	Comment noted
	British Association of Urological Surgeons	moderately urgent	Comment noted. No changes to the scope required.
	Royal college of pathologists	No Comments	Comment noted
	Royal college of physicians	Potentially important	Comment noted. No changes to the scope required.
	NCRI Breast Clinical Studies Group	Not-urgent. Some of the relevant data are only available in abstract form.	Comment noted. No changes to the scope required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Amgen	The background information in the current appraisal scope does not accurately describe the patient population and current treatment options that is the subject of this proposed appraisal. Within the disease continuum of prostate cancer, prior to the development of metastases, distinct non-metastatic clinical states exist which are characterised by differences in hormonal manipulation response status and associated risks for skeletal complications. These states which can occur in sequence and vary in duration include a castration sensitive non-metastatic phase with a low risk for developing bone metastases and, a castration resistant non-metastatic phase with a high risk for developing bone metastases.	Comments noted. The scoping document only provides a very brief summary of the condition and its management.
	Amgen	It should also be noted that the population for this appraisal is best described as castration/castrate-resistant rather than hormone-refractory.[1]	Comments noted. The background of the scope has been amended accordingly
	Amgen	Amgen recommends that the background information in the current appraisal scope is adapted to provide appropriate accuracy and completeness of information for castrate-resistant non-metastatic prostate cancer patients at increased risk of bone metastasis.	Comments noted. The scoping document only provides a very brief summary of the condition and its management.

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	British Association of Urological Surgeons	The background information is basically accurate but it fails to acknowledge some important points from the study recently completed: 1) The patients on average had very high PSA levels at study entry (median 346ng/L) 2) The average age of the patients at study entry was 74. 3) The ECOG performance status was 1 in 99% of the patients	Comments noted. The scoping document only provides a very brief summary of the condition and its management. Details of the relevant clinical trials will be assessed during the appraisal.
	Royal college of pathologists	No comments	Comment noted
	Royal college of physicians	Consider changing last paragraph to: Between 70-80% of men present with non-metastatic prostate cancer. Of these, approximately 55% to 60% progress to metastatic disease. The prognosis is poor for men with hormone-refractory metastatic prostate cancer; survival is not expected to exceed 15 months. The aim of treatment at this point is to alleviate symptoms, prolong life and slow progression of the disease. NICE Technology Appraisal No. 101 recommends docetaxel as a treatment option for men with hormone-refractory metastatic prostate cancer who have a Karnofsky performance-status score of 60% or more. For men with hormone-refractory metastatic prostate cancer that has progressed during or after a docetaxel-based treatment, patients may receive a combination of palliative treatments.	Comments noted. The background of the scope has been amended accordingly.
	NCRI Breast Clinical Studies Group	Adequate, but see below.	Comment noted. The scoping document only provides a very brief summary of the condition and its management.

Section	Consultees	Comments	Action
The technology/ intervention	Amgen	Amgen wishes to highlight that the proprietary name stated for denosumab (Prolia®) in the current appraisal scope is incorrect. Denosumab is available as two different medicinal products with different dosing regimens and formulations that reflect their respective therapeutic applications. Prolia® is the proprietary name for denosumab for the following licensed indications: ▪ Treatment of osteoporosis in postmenopausal women at increased risk of fractures ▪ Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures XGEVA® is the proprietary name for denosumab for the following licensed indication: ▪ The prevention of skeletal-related events in adults with bone metastases from solid tumours (subject of an ongoing NICE multiple technology appraisal) The proprietary name XGEVA® is anticipated to apply to the planned indication for denosumab for the treatment of men with castrate-resistant prostate cancer at high-risk of developing bone metastases. Denosumab prolongs bone metastasis-free survival by reducing the risk of developing bone metastases.Amgen kindly request that the proprietary name is changed to XGEVA® in the appraisal scope.	Comments noted. The technology section of the scope has been amended accordingly.

Section	Consultees	Comments	Action
	British Association of Urological Surgeons	Basically, yes, although the description is quite limited	Comments noted. The scoping document only provides a very brief summary of the condition and its management.
	Royal college of pathologists	No comments	Comment noted
	Royal college of physicians	Yes but consider changing second paragraph to: Denosumab does not hold a UK marketing authorisation for prolonging bone metastasis-free survival in men with hormone-refractory prostate cancer. It has been studied in a clinical trial compared with placebo to prolong bone metastasis-free survival (that is, time to first occurrence of bone metastasis or death) in men with hormone-refractory (androgen independent) non-metastatic prostate cancer who are considered to be at high risk for the development of bone metastases. The trials define individuals as high risk of bone metastases if their prostate specific antigen (PSA) level is greater than or equal to 8.0ng/mL, or their PSA level doubles within 10 months.	Comments noted. The technology section of the scope has been amended accordingly.
Population	Amgen	Amgen recommends that the term castrate-resistant (rather than hormone-refractory) prostate cancer is used to describe this patient population	Comments noted. The population in the scope have been amended accordingly.
	British Association of Urological Surgeons	See comments above in the section "background". There is also some uncertainty as to how to define "Castrate resistant disease". The parameters for this have not been recognised internationally. The usual definition is for advancing disease measured clinically or on PSA rise notwithstanding the use of first and second line hormone therapy but the definition of clinical or PSA progression is not currently set at a defined cut off.	Comments noted.

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	Royal college of pathologists	No comments .	Comment noted.
	Royal college of physicians	A difficult population to define. The high risk classification used is reasonable based on PSA DT and PSA . In time however most patients with castration resistent ca prostate will develop metastases and we would consider making the population any patient with castration resistant non-metastatic prostate cancer	Comment noted. The manufacturer confirmed at the scoping workshop that the registration clinical trial on which the marketing authorisation is based defined high risk of developing bone metastases as the presence of prostate-specific antigen (PSA) 8ng/ml or a PSA doubling time of ≤ 10 months. There was consensus amongst the consultees at the scoping workshop that this definition of high risk was appropriate.

Section	Consultees	Comments	Action
Comparators	Amgen	To date, no other therapy than denosumab has shown to be effective in delaying the development of bone metastasis in men with castrate-resistant prostate cancer. Therefore, in the context of this pre-metastatic disease state and current care within the NHS, best supportive care currently constitutes continuation of androgen deprivation therapy with observation and follow-up of patients with castrate-resistant prostate cancer until bone metastasis occur. Amgen recommends that the appropriate comparator for the prevention of bone metastasis in castrate-resistant prostate cancer is defined as best supportive care.	Comment noted. Consultees also agreed that bisphoshonates should be included as a comparator in the scope. The consultees agreed that although bisphononates do not have a marketing authorisation for the treatment or prevention of bone metastatasis in prostate cancer, nor was there any NICE guidance recommending their use in the treatment of prostate cancer, they are widely used in UK clinical practice. However, it appeared possible that bisphosphonates may be used at this stage in the treatment pathway in the near future, depending out results from ongoing research.

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	British Association of Urological Surgeons	Best alternative care may be used although technically, this therapy would be used in parallel with other therapies for CRPC, particularly the use of chemotherapy in M0 disease with a high and rapidly rising PSA. The question of use in conjunction with Abiraterone (see above) is unresolved. It should also be borne in mind that only about 30% of UK patients receive chemotherapy as part of their treatment for CRPC.	Comment noted. During the scoping workshop consultees explained that all people with non-metastatic prostate cancer would receive best supportive care and that best supportive care could also include treatment with denosumab. Consultees therefore agreed that the comparator included in the scope should specify it was best supportive care without denosumab. The consultees agreed at the scoping workshop that chemotherapy is not used to treat non-metastatic prostate cancer in UK clinical practice, and therefore chemotherapy should not be included as a comparator in the scope. Consultees agreed at the scoping workshop that abiraterone should not be a comparator in the scope because it would be used at a different point in the treatment pathway than denosumab or it may be used in conjuction with denosumab in UK clinical practice. Continued…

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			Consultees also agreed that bisphoshonates should be included as a comparator in the scope. The consultees agreed that although bisphononates do not have a marketing authorisation for the treatment or prevention of bone metastatasis in prostate cancer, nor was there any NICE guidance recommending their use in the treatment of prostate cancer, they are widely used in UK clinical practice. However, it appeared possible that bisphosphonates may be used at this stage in the treatment pathway in the near future, depending out results from ongoing research.
	Royal college of pathologists	No comments .	Comment noted
	Royal college of physicians	This is a relatively uncommon condition and patients are often treated as part of a clinical trial. We are not sure there is a consensus on treatment for this group of men. Options are docetaxel immediate v deffered v further atttempt at hormone manipulation with stilboestrol v observation	Comment noted. It was agreed at the scoping workshop that 'best supportive care without denosumab' and 'bisphosphonates' were the most appropriate comparators.

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	British Association of Urological Surgeons	Furthermore, the new technology, Abiraterone, is technically a hormone therapy and this is also like to be used widely in "Castrate resistant disease". The place and timing of denosumab for this indication needs to be considered in the Abiraterone era.	Consultees agreed at the scoping workshop that abiraterone should not be a comparator in the scope because it would be used at a different point in the treatment pathway than denosumab or it may be used in conjuction with denosumab in UK clinical practice. .
Outcomes	Amgen	In order to capture the most important and relevant health-related benefits (and harms) for the population in this indication, Amgen recommends the following outcome measures should be included in the appraisal scope: ▪ Bone metastases-free survival ▪ Time to development of bone metastases ▪ Overall survival ▪ Adverse effects of treatment Health-related quality of life	Comments noted. It was agreed at the scoping workshop that Time to first occurrence of bone metastasis, time to first symptoms, time to first treatment intervention , bone metastasis free survival, overall survival, adverse effects of treatment, and health-related quality of life were the most appropriate outcomes.
	British Association of Urological Surgeons	The outcome measures seems appropriate	Comment noted. No changes to the scope required.
	Royal college of pathologists	No comments	Comment noted.

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	Royal college of physicians	Reasonable but also consider time to first intervention such as external radiation therapy , surgery, opiates, change in systemic therapy. If treatment delays symptomatic bone mets then still useful	Comments noted. It was agreed at the scoping workshop that Time to first occurrence of bone metastasis, time to first symptoms, time to first treatment intervention , bone metastasis free survival, overall survival, adverse effects of treatment, and health-related quality of life were the most appropriate outcomes.
Economic analysis	Amgen	No comment	Comment noted.
	British Association of Urological Surgeons	It will be important to consider the cost of treatment of bone metastases and in particular, the complications arising therefrom, particularly pathological fracture and cord compression. The HR for reduction of Symptomatic bone metastases for the study recently conducted was 0.67.	Comment noted. No changes to the scope required.
	Royal college of pathologists	No comments	Comment noted.
	Royal college of physicians	Ok	Comment noted.
Equality and Diversity	Amgen	No comment	Comment noted.
	British Association of Urological Surgeons	Not applicable	Comment noted.
	Royal college of pathologists	None	Comment noted.
	Royal college of physicians	No concerns	Comment noted

Section	Consultees	Comments	Action
Other considerations	Amgen	No comments	Comment noted.
	British Association of Urological Surgeons	The risk of bone metastases should be considered. Patients with high grade disease (8-8+) with short PSA doubling times and patients with PSA levels >50ng/ml are an especially high risk group. There should also be a counterbalancing risk for consideration of developing the complication of "osteonecrosis of the jaw". The rate of this was 4% in the study but r	Comment noted. The manufacturer confirmed at the scoping workshop that the registration clinical trial on which the marketing authorisation is based defined high risk of developing bone metastases as the presence of prostate-specific antigen (PSA) 8ng/ml or a PSA doubling time of ≤ 10 months. There was consensus amongst the consultees at the scoping workshop that this definition of high risk was appropriate.
	Royal college of pathologists	None	Comment noted

Section	Consultees	Comments	Action
	Royal college of physicians	Possibility of drugs such as abiraterone or MDV3100 may be an option for men in this population	Consultees agreed at the scoping workshop that abiraterone was not an appropriate comparator because it would be used at a different point in the treatment pathway than denosumab or it may be used in conjuction with denosumab in UK clinical practice. Consultees agreed at the scoping workshop that MDV3100 is not an appropriate comparator because it is currently only in the experimental stage and therefore years away from potentially receiving a marketing authorization.

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Questions for consultation (Innovation)	Amgen	There are currently no therapies available that reduce the risk of bone metastasis in men with castrate-resistant prostate cancer. Denosumab offers a new therapeutic approach that can prevent or delay bone metastases and subsequent declines in health status (including development of skeletal complications). Denosumab is the first and only therapy to target the biological mechanism of bone loss. It is a fully human monoclonal antibody (IgG2) that binds with high affinity to receptor activator of nuclear factor kappa-B ligand (RANK-L), which is a key mediator in the cycle of bone destruction through control of osteoclast formation, function and survival. Suppression of bone resorption by blocking osteoclastic activity (i.e., RANKL inhibition) has beenhypothesised to delay the establishment and progression of skeletal tumours. Amgen Study 20050147 (Phase III randomised control trial) is the first study in prostate cancer to show that manipulation of the bone microenvironment with denosumab (120mg every four weeks) prevents progression to bone metastasis - the most common site of disease progression in patients who are castrate-resistant and have not yet developed metastatic disease. In addition, the selection of high risk patients for treatment using PSA values or, PSA doubling time as a biomarker prior to the development of bone metastases allows the treatment to b given for those patients most at risk and supports the innovative nature of this approach.[1,2] As a result of its unique and specific mechanism of action in blocking RANK-L activity, denosumab has the potential to fulfil an unmet medical need to prolong bone metastasis-free survival in men with castrate-resistant prostate cancer at high risk of developing bone metastasis. The delay of metastasis to the bone, the predominant location of distant spread from prostate cancer, will result in a delay in of metastatic therapies such as chemotherapy or additional hormonal manipulation. medical step-change in the management of the condition.	Comment noted. No changes to the scope required.

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		Amgen therefore believes that the innovation provided by denosumab in prolonging bone metastases-free survival in men with castrate-resistant prostate cancer, represents a medical step-change in the management of the condition.	
	British Association of Urological Surgeons	The technology is innovative. This is a new class of drug and it has been shown in a well constructed and appropriately prowered study, for the first time, to reduce the bone metastasis rate in prostate cancer patients. The reduction is relatively modest overall but the rate of reduction in those patients going on to develop symptomatic bone metastases is significant (a 33% reduction overall in this subgroup). The technology is a modest step change. The use of the technology may result in health related benefits. QALY considerations should take in to account the morbidity associated with pathological fracture and cord compression, which are often devastating and costly complications. There is a significant literature available on the effects of bone metastasis and the complications arising therefrom. There are 3 high quality studies in prostate cancer in relation to this technology (bone mass preservation in androgen deprivation, reduction in complications in patients with established bone mets and the recent study of bone met rate reduction. There are other studies in different cancer types.	Comment noted. No changes to the scope required.
	Royal college of pathologists	There is a need to look at the evidence with regard to the effectiveness of denosumab in preventing bone metastases. The cost of denosumab has not been addressed Subgroups of pateints (i.e. patients with high gleason scores - 9/10) should also be addressed	Comment noted. No changes to the scope required.
	Royal college of physicians	This depends on the published data. If there is a clinically significant delay in the onset on bone metastases in high risk patients, this would be a significant change in the treatment	Comment noted. No changes to the scope required.

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		paradigm for this cohort of patients. Yes important as bone disease has a significant impact on QoL. There is also an onoging cost to the NHS through use of analgesics, surgery, pallaiitve radiotherapy etc to treat symptoms. Unlike iv bisphoshonates this is a sc injection and could be given in primary care. There is less need for associated medical costs to provide the treatment in a hospital setting	
How should hormone-refractory prostate cancer be defined	Amgen	Amgen recommends that castrate-resistant prostate cancer should be defined as evidence of a rising PSA in patients who in a castrate state induced either by surgical orchiectomy or medical androgen deprivation therapy.	Comment noted. It was agreed at the scoping workshop that population in the draft scope should be "People with non-metastatic castrate resistant prostate cancer at high risk (PSA ≥8ng/mL or PSA doubling time ≤ 10 months) of developing bone metastases".
	British Association of Urological Surgeons		
Should high risk of bone metastases be included in the population of the scope, and how should it be defined?	Amgen	Patients with a high risk of bone metastases should be included as the population within the appraisal scope. The risk for developing bone metastases is extremely high in patients who are castrate-resistant and present with either high baseline prostate specific antigen (PSA) and/or aggressive PSA-kinetics as evidenced from short PSA doubling times. Amgen recommends that patients with castrate-resistant prostate cancer at high risk of bone metastasis be defined as patients with elevated PSA values 8 ng/mL or higher or PSA doubling times of 10 months or less	It was agreed at the scoping workshop that population in the draft scope should be "People with non-metastatic castrate resistant prostate cancer at high risk (PSA ≥8ng/mL or PSA doubling time ≤ 10 months) of developing bone metastases".

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	British Association of Urological Surgeons	Definitely. Gleason 8 and 8+. PSA's above 50 and M0. Rapidly rising PSA's above 20 in men below 65.	It was agreed at the scoping workshop that population in the draft scope should be "People with non-metastatic castrate resistant prostate cancer at high risk (PSA ≥8ng/mL or PSA doubling time ≤ 10 months) of developing bone metastases".
Where does denosumab for prolonging bone metastases-free survival fit into the current treatment pathway for hormone-refractory prostate cancer? *Is this treatment for non-metastatic disease only?* *If so, what is the clinical consensus on the current treatment of non-metastatic hormone-refractory prostate cancer?*	Amgen	For patients with non-metastatic castrate-resistant prostate cancer, the goals of treatment are to prevent the development of metastatic disease while at the same time maintaining quality of life Bone metastases are the most common site of metastases in prostate cancer, develop in up to 90% of patients with advanced prostate cancer. The risk of developing bone metastases is increased in patients with castrate-resistant prostate cancer who present with either high baseline prostate specific antigen (PSA) and/or aggressive PSA kinetics such as short PSA doubling times.[1] To date, no other therapy than denosumab has shown to be effective in delaying the development of bone metastasis in men with castrate-resistant prostate cancer. Denosumab (if licensed) is anticipated to fit into the treatment pathway of castrate-resistant disease in patients at high risk prior to the development of bone metastases.	Comment noted. Comment noted. No changes to the scope required.
	British Association of Urological Surgeons	Denosumab is also used for bone preservation following androgen deprivation (at reduced dose and dosing frequency) and for reduction in the rate of skeletal related events in established metastases (at the same dose and frequency as for metastasis prevention). There is no firm consensus on the management of CRPC. Most get further hormones, a proportion get chemotherapy and a significant number are likely to receive Abiraterone therapy. Poor performance and elderly patients usually receive best supportive care	Comment noted. Comment noted. No changes to the scope required.

Section	Consultees	Comments	Action
	Royal college of physicians	We do not believe denosumab has yet established a role in non-metastatic prostate cancer.	Comment noted. Comment noted. No changes to the scope required.
What is the size of the potentially eligible patient population in UK clinical practice?	Amgen	In England and Wales, there are an estimated 190,000 patients with prostate cancer. Patients with castrate-resistant non-metastatic prostate cancer and who are at high risk for developing bone metastases are anticipated to be a small proportion of the overall prostate cancer patient population. An estimate of the size of the patient population in the UK is not currently available. Amgen are undertaking epidemiological research and will provide the Institute this information once available.	Comment noted. Comment noted. No changes to the scope required.
	British Association of Urological Surgeons	Quite difficult to gauge accuratley. 10.5K deaths annually and most will have bone mets. About 10% have these at first presentation. Probably about 9K men at risk per year: this would have to be reduced to factor in poor performance and PSA's at a much lower level. Probably about a 40 to 50% reduction on this total.	Comment noted. Comment noted. No changes to the scope required.
	Royal college of physicians	This would be the incident population with high risk features, for which statistics are not readily available. However, most of the men who die of prostate cancer have bone metastases, so the order of magnitude is likely to be around 8-9,000 per year in the UK.	Comment noted. Comment noted. No changes to the scope required.

Section	Consultees	Comments	Action
Is best supportive care the most appropriate comparator for denosumab for prolonging bone metastases-free survival in men with hormone-refractory prostate cancer? How should best supportive care be defined?	Amgen	To date, no other therapy than denosumab has shown to be effective in delaying the development of bone metastasis in men with castrate-resistant prostate cancer. In the context of this disease state and current care within the NHS; best supportive care currently constitutes continuation of androgen deprivation therapy and observation and follow-up of patients until bone metastasis occur. There are no therapies that have demonstrated benefit in delaying the onset of bone metastases in patients with castrate-resistant prostate cancer. Based on current usage patterns there are also no therapies commonly used to delay the onset of bone metastases.	Comment noted. It was agreed at the scoping workshop that 'best supportive care without denosumab' and 'bisphosphonates' were the most appropriate comparators.
Are anti-androgens commonly used to delay the onset of metastases in people with hormone-refractory prostate cancer in the UK? If so, which agents are commonly prescribed?		Anti-androgens are recommended for the management of patients with locally advanced prostate cancer at high risk of disease progression. As stated in the NICE clinical guideline (CG58), prostate cancer can be considered to be hormone refractory when androgen withdrawal therapy or combined androgen blockade are no longer controlling the prostate specific antigen (PSA), or the symptoms of the disease, or when there is radiological evidence of progression.[1] The Phase III clinical trial of denosumab (Study 20050147) was conducted in a population with castrate-resistant prostate cancer in which androgen deprivation therapy was no longer controlling PSA levels.hemotherapy (docetaxel) with or without corticosteroids is currently indicated and also recommended by the Institute for the treatment of patients with metastatic hormone-refractory prostate cancer.[1,2] Since the population under consideration in this appraisal is largely non-metastatic castrate-resistant prostate cancer (lymph node metastasis was allowed, but only less than 13% of patients had lymphatic involvement at baseline), the inclusion of chemotherapy as a comparator in this non-metastatic population is inappropriate. Amgen recommends that the appropriate comparator for the prevention of bone metastasis in castrate-resistant prostate cancer is defined as best supportive care.	Comment noted. No changes to the scope required.
Should chemotherapy (with or without corticosteroids) be included as a comparator?			Comment noted. Consultees agreed at the scoping workshop that chemotherapy is not used to treat non-metastatic prostate cancer in UK clinical practice and therefore should not be a comparator in the scope.
			Comment noted. No

Section	Consultees	Comments	Action
	Royal college of physicians	For pre-metastatic patients, best supportive care usually involves adding and substracting anti-androgens, and using further lines of hormones e.g. Dexamethasone as well as supporting and managing treatment toxicity (eg metabolic syndrome).	
Are there any subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately?	Amgen	An assessment of the pre-defined subgroups or any other subgroups in which denosumab may be expected to be more clinically and cost effective is currently under evaluation.	Comment noted.
	Royal college of physicians	No	Comment noted. No changes to the scope required.

Section	Consultees	Comments	Action
Denosumab for the treatment of therapy-induced bone loss in non-metastatic prostate cancer is subject to terminated NICE guidance (No. 194). Are the populations in guidance No. 194 and the proposed appraisal of denosumab for prolonging bone metastasis-free survival similar? If they are similar patient populations should NICE combine these appraisals in a single appraisal in order to consider all health effects relevant to patients?	Amgen	The prostate cancer patient populations, planned indications and treatment intent are different for that of denosumab in therapy-induced bone loss in non-metastatic prostate cancer (Technology Appraisal 194) and the proposed appraisal in castrate-resistant prostate cancer.In the evaluation of denosumab for the treatment of **therapy-induced bone loss in non-metastatic prostate cancer** (Technology Appraisal 194): ▪ Patients are required to have prostate cancer sensitive to androgen deprivation therapy (ADT), with stable PSA values, indicating effective control of the underlying prostate cancer by ADT. ▪ Patients are treated with denosumab (Prolia®) 60mg every 6 months: The therapy-inducted bone loss in this patient population is characterised by an imbalance of bone remodelling favouring bone resorption and is reflected by slightly elevated bone turnover markers affecting all bones. This requires chronic treatment with a dose and frequency of denosumab sufficient to suppress elevated bone resorption. Pharmacokinetic and pharmacodynamic studies have shown that denosumab (Prolia®) 60 mg every 6 months is the optimal dose for this disease area.In the evaluation of denosumab as treatment for **prolonging bone metastases free survival in patients with castrate-resistant prostate cancer** (proposed appraisal): ▪ Patients are required to have castrate-resistant prostate cancer, characterised by three consecutive rising PSA values during ADT, indicating that ADT no longer controls prostate cancer cells. ▪ Patients are treated with denosumab (XGEVA®) 120mg every 4 weeks: A higher dose is required in order to achieve maximum suppression of bone turnover in order to manipulate the bone microenvironment so that tumour cells are unable to drive bone turnover towards excessive local resorption and resulting macroscopic bone metastases. Should this topic be formally referred by the Department of Health for appraisal by the Institute; Amgen recommend that separate appraisals of denosumab are required to	Comment noted. No changes to the scope required.

Section	Consultees	Comments	Action
	Royal college of physicians	There will be some overlap as both groups include high risk patients. However the population for guidance No. 194 is significantly larger, and includes men with localised disease receiving 2-3 years + of adjuvant hormone therapy. If they are similar patient populations should NICE combine these appraisals in a single appraisal in order to consider all health effects relevant to patients? We strongly believe that these are completely separate issues and should remain so.	Comment noted. No changes to the scope required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope:

Healthcare Improvement Scotland (formerly known as NHS Quality Improvement Scotland)

Marie Curie Cancer Care

Royal College of Nursing

Welsh Government

Department of Health

Medicines and Healthcare products Regulatory Agency

Comment 3: the provisional matrix

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	*Proposal made by:*		*Action taken:* Removed/Added/Not included/Noted	*Justification:*
1.	Remove CANCERactive from patient/carer group consultees.	NICE Secretariat		Removed	This organisation has disbanded. CANCERactive has been removed from the matrix of consultees and commentators
2.	Remove Chinese National Healthy Living Centre from patient/carer group consultees.	NICE Secretariat		Removed	Chinese Healthy Living Centre have requested that they only be contacted about Chinese-related business (BME topics, Hep B, vaccination, retaining organs)
3.	Add Allied Health Professional Federation to general commentators	NICE Secretariat		Added	Allied Health Professionals Federation meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a general group commentator.

4.	Remove Prostate Action from research groups	NICE Secretariat		Removed	Prostate Action merged with Prostate Cancer UK who are already included in Patient/carer groups.
5.	Remove Prostate Cancer Research Foundation from research groups	NICE Secretariat		Removed	Prostate Cancer Research Foundation merged with Prostate UK to become Prostate Action.
6.	Add the Urology Foundation to professional groups	NICE Secretariat		Added	The Urology Foundation meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a professional group consultee.
7.	Add Prostate Cancer Support Association	Amgen		Not included	The Prostate Cancer Support Association disbanded in June 2010.
8.	Add British Institute of Musculoskeletal Medicine to professional groups	NICE Secretariat		Added	The British Institute of Musculoskeletal Medicine meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a professional group.

9.	Add British Orthopaedic Association to professional groups	NICE Secretariat		Added	The British Orthopaedic Association meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a professional group.
10.	Add the British Society of Skeletal Radiologists to professional groups	NICE Secretariat		Added	The British Society of Skeletal Radiologists meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a professional group.
11.	Add the Independent Cancer Patients' Voice to patient/carer groups	NICE Secretariat		Added	The Independent Cancer Patients' Voice meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a research group.
12.	Add NHS England to consultee other.	NICE Secretariat		Added	NHS England meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a research group.