A systematic review and economic model of the effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer

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CRD/CHE Technology Assessment Group

The Technology Assessment Group at the University of York is drawn from two specialist centres: the Centre for Reviews and Dissemination (CRD) and the Centre for Health Economics (CHE).

CRD undertakes reviews of research about the effects of interventions used in health and social care (www.york.ac.uk/inst/crd). The centre maintains various databases, provides an enquiry service and disseminates results of research to NHS decision makers.

CHE undertakes research and training in all areas of health economics (www.york.ac.uk/inst/che). The bulk of the input into the TARs comes from the Team for Economic Evaluation and Health Technology Assessment (TEEHTA) which specialises in decision analysis and Bayesian methods in economic evaluations (see http://www.york.ac.uk/inst/che/teehta.htm).

Recent TARs undertaken by CRD/CHE at York relate to efalizumab and etanercept for the treatment of psoriasis; etanercept and infliximab for the treatment of psoriatic arthritis; topotecan, pegylated liposomal doxorubicin hydrocholoride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer; methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder; and clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events.

Contributions of authors

Ros Collins	Lead reviewer responsible for writing the protocol, study selection, data extraction, validity assessment and writing the final report.
Elisabeth Fenwick	Involved in the cost-effectiveness section, writing the protocol, study selection, data extraction, development of the economic model and report writing.
Rebecca Trowman	Reviewer involved in the clinical effectiveness section, involved in study selection, data extraction, validity assessment and writing the final report.
Rodolphe Perard	Involved in the cost-effectiveness section, study selection, data extraction, development of the economic model, review of quality of life studies and report writing.
Gill Norman	Reviewer involved in the clinical effectiveness section, involved in study selection, data extraction and validity assessment.
Kate Light	Devised the search strategy and carried out the literature searches; wrote the search methodology sections of the report.
Alison Birtle	Provided clinical advice and commented on drafts of the report.
Stephen Palmer	Provided input at all stages, involved in the development of the economic model, commented on drafts of the report; overall responsibility for the cost-effectiveness section of the report.
Rob Riemsma	Provided input at all stages, commented on drafts of the report; overall responsibility for the clinical effectiveness section of the report.

Conflicts of interest

Rodolphe Perard has previously undertaken an internship with Sanofi-Aventis as part of a Master's course in project management. This project was on unrelated products. None of the other authors have conflicts of interest to report.

Relationship of reviewer(s) with sponsor

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Executive summary

Background

Prostate cancer is the most common male cancer, excluding non-melanoma skin cancer, in the UK, accounting for around 13% of male cancer deaths. In 2001, there were 26,027 new cases in England and 1,746 in Wales, giving age standardised incidence rates of 89.8 and 92.6 per 100,000 men respectively. The majority of prostate cancers initially respond to hormone therapy, with a median response duration in metastatic disease of around 18 months. However, in most patients the cancer will become resistant to hormonal treatment and will progress. After developing hormone resistant disease, survival is not expected to exceed 9 to 12 months. Treatment for metastatic hormone-refractory prostate cancer (mHRPC) is palliative and current advice issued by NICE states that chemotherapy should be considered and trials of chemotherapy supported, while palliative radiotherapy should also be considered as a treatment option. The use of chemotherapy for mHRPC is widespread in the UK. New trials assessing the effectiveness of docetaxel for the treatment of mHRPC, which is licensed for use in combination with prednisone/prednisolone in the UK, have emerged. Therefore the evidence must be appraised by a systematic review and economic model.

Objectives of the review

A systematic review was undertaken and an economic model constructed to evaluate the clinical effectiveness and cost-effectiveness of docetaxel (Taxotere®, Sanofi-Aventis) in combination with prednisone/prednisolone for the treatment of mHRPC. The main comparators considered were other chemotherapy regimens and best supportive care.

Methods

Search strategy: A scoping search was conducted which identified a study of docetaxel plus prednisone versus mitoxantrone (Novantrone®, Wyeth) plus prednisone. The scoping search did not identify any trials comparing docetaxel plus prednisone/prednisolone with any of the other relevant treatments. However, trials comparing mitoxantrone with other chemotherapies and corticosteroids (used as best supportive care) were identified. Therefore, in order to allow for a comparison

between docetaxel and other relevant treatments, the clinical effectiveness and cost-effectiveness of mitoxantrone, the common comparator were also reviewed.

Twenty-one databases were searched for randomised controlled trials (RCTs) and systematic reviews of the clinical effectiveness of docetaxel and mitoxantrone and economic evaluations of the cost-effectiveness of docetaxel and mitoxantrone.

Inclusion/exclusion criteria: Two reviewers independently screened all titles and/or abstracts including economic evaluations. The full manuscript of any study judged to be relevant by either reviewer was obtained and assessed for inclusion or exclusion. Disagreements were resolved through discussion. For the assessment of clinical effectiveness RCTs that compared docetaxel in combination with prednisone/prednisolone with any chemotherapy regimen or best supportive care (which may include radiotherapy, corticosteroids, oxygen, antibiotics and analgesics) or placebo were included. RCTs that assessed mitoxantrone in combination with a corticosteroid compared with any chemotherapy regimen or best supportive care or placebo, were also eligible for inclusion. For the assessment of cost-effectiveness, a broader range of study designs were considered.

Data extraction and quality assessment: Data from included studies were extracted by one reviewer and independently checked for accuracy by a second reviewer. Individual studies were assessed for quality by one reviewer and independently checked for accuracy by a second reviewer.

Methods of analysis/synthesis: The results of the data extraction and quality assessment for each study of clinical effectiveness are presented in structured tables and as a narrative summary. Where appropriate, outcomes were synthesised using formal analytic approaches. For the cost-effectiveness section of the report, details of each identified published economic evaluation, together with a critical appraisal of its quality, are presented in structured tables. A new cost-effectiveness model was developed in order to establish the cost-effectiveness of docetaxel compared with a range of potential comparators.

Handling the company submissions: No substantive additional clinical effectiveness data were presented in the company submission. The economic evaluation included in the company submission was assessed and used to inform the development of the new model.

Results

A total of 1065 titles and abstracts were screened for inclusion in the review of clinical and cost-effectiveness and 267 records were ordered as full papers. Seven RCTs were identified that met our inclusion criteria. Three of these trials used docetaxel compared to mitoxantrone plus prednisone, three trials used mitoxantrone plus a corticosteroid compared to a corticosteroid and one trial used mitoxantrone plus prednisone compared to mitoxantrone plus prednisone plus clodronate.

Clinical effectiveness

We found one trial that assessed the intervention under consideration: docetaxel plus prednisone; this was in comparison with mitoxantrone plus prednisone (TAX 327). No other trials were found that assessed the clinical effectiveness of docetaxel plus prednisone. The results of this trial showed statistically significant improvements with 3-weekly docetaxel plus prednisone compared with mitoxantrone plus prednisone, in terms of overall survival, quality of life, pain response, and PSA decline. Response rate was higher for the 3-weekly docetaxel plus prednisone group than the mitoxantrone plus prednisone group, but this difference was not statistically significant. The improved outcomes for docetaxel plus prednisone were associated with more grade 3-4 adverse events; however, this had no detrimental effect on quality of life, which was also significantly improved in the 3-weekly docetaxel group. Progression-free survival was not assessed in this trial.

Since docetaxel plus prednisone is only compared with mitoxantrone plus prednisone, it was considered important to consider other evidence which would inform a comparison against other potentially relevant comparators (e.g. other chemotherapy-based treatments and best supportive care). Therefore, we searched for all other treatments that were compared with mitoxantrone plus a corticosteroid.

We found three trials comparing mitoxantrone plus prednisone with another chemotherapy regimen: one trial that compared mitoxantrone plus prednisone with docetaxel plus prednisone plus estramustine; one trial that compared mitoxantrone plus prednisone with docetaxel plus estramustine; and one trial that compared mitoxantrone plus prednisone with mitoxantrone plus prednisone plus clodronate. Both treatments that included docetaxel were superior to mitoxantrone plus prednisone in terms of overall survival (although the difference was not statistically significant for docetaxel plus prednisone plus estramustine), response rate (although the difference was not statistically significant for docetaxel plus estramustine), and progression-free survival (although this was only assessed for docetaxel plus estramustine in comparison with mitoxantrone plus prednisone). Docetaxel plus estramustine was associated with more adverse events, compared with mitoxantrone plus prednisone. No significant differences were found between mitoxantrone plus prednisone plus clodronate and mitoxantrone plus prednisone without clodronate.

In addition, we found three trials that compared mitoxantrone plus a corticosteroid with best supportive care, i.e. corticosteroids. Two of these used prednisone (5 mg twice daily) as the comparator, while one compared mitoxantrone plus hydrocortisone with hydrocortisone (40 mg given in two divided doses daily). One of the trials included men with asymptomatic mHRPC; another included men with symptomatic mHRPC, with symptoms including pain and disease progression; while the third study included all men with progressive mHRPC. One trial allowed patients to cross over during the trial, this resulted in 50 out of 81 patients randomised to prednisone to receive additional mitoxantrone; the other two trials did not allow crossovers.

The combined result of these three trials showed very little difference between mitoxantrone plus corticosteroids compared with corticosteroids alone in terms of overall survival (HR=0.99 [95% CI: 0.82, 1.20]). Other outcomes could not be pooled because they were measured differently in the three trials. However, in the two studies that measured health-related quality of life and pain responses, the mitoxantrone groups had statistically significant improvements compared with the corticosteroid groups. Due to the limited follow-up for these outcomes these benefits should not be overstated.

An adjusted indirect comparison was performed to estimate the relative efficacy of docetaxel plus prednisone versus corticosteroids. The results of the indirect comparison showed that docetaxel plus prednisone seems to be superior to prednisone alone in terms of overall survival. However, this is based on an indirect comparison using one good quality trial comparing docetaxel plus prednisone with mitoxantrone plus prednisone (TAX 327) and three trials comparing mitoxantrone plus corticosteroids with corticosteroids, that differed in terms of patient population and methodology.

In summary, a direct comparison of docetaxel plus prednisone versus mitoxantrone plus prednisone in an open-label randomised trial showed improved outcomes for docetaxel plus prednisone. Two other chemotherapy regimens that included docetaxel: docetaxel plus estramustine and docetaxel plus prednisone plus estramustine, also showed improved outcomes in comparison with mitoxantrone plus prednisone. Mitoxantrone plus prednisone plus clodronate showed no significant differences in comparison with mitoxantrone plus prednisone. Our review of the data suggests that docetaxel plus prednisone is the most effective treatment for men with mHRPC.

Cost-effectiveness

The systematic literature search identified only one study which met the criteria for inclusion in the cost-effectiveness review. A separate cost-effectiveness analysis was also submitted by the manufacturers (Sanofi-Aventis).

Of the cost-effectiveness evidence reviewed, only the manufacturer's submission was considered directly relevant from the perspective of the NHS. The review of this evidence highlighted potential limitations within the submission in its use of data, the range of comparators considered and the lack of quality-adjustment in the final outcome. These limitations led to the development of a new model with the aim of providing a more comprehensive range of comparators (including a comparison with other chemotherapy regimens and prednisone/prednisolone alone) for the analysis of the cost-effectiveness of docetaxel plus prednisone/prednisolone from the perspective

of the UK NHS. Two separate analyses were undertaken based on different sets of potentially relevant comparators. Despite the use of separate analyses, the estimates of cost-effectiveness provided in both analyses were identical. This model indicated that mitoxantrone plus a corticosteroid dominates a corticosteroid alone (i.e. it is cheaper and more effective). Compared to mitoxantrone plus prednisone/prednisolone, the use of docetaxel plus prednisone/prednisolone (3-weekly) appears cost-effective as long as the NHS is willing to pay £32,706 per QALY. A range of sensitivity analyses were undertaken to test the robustness of the model to alternative assumptions regarding discount rates, quality of life estimates and the impact of side effects. The ICER associated with D+P (3-weekly) remained fairly robust to these variations with estimates ranging from £28,019 to £33,298 per QALY. Value of information analysis revealed that further research is potentially valuable. Given a maximum acceptable ratio of £30,000 per QALY the expected value of information was estimated to be approximately £13.36 million.

Conclusions

Clinical effectiveness

The evidence demonstrates that docetaxel plus prednisone is superior to mitoxantrone plus prednisone, in terms of overall survival, quality of life, pain, and PSA decline. Docetaxel plus prednisone seems to be superior to corticosteroids alone in terms of overall survival. However, this is based on an indirect comparison; therefore, the results need to be interpreted with some caution. Our review of the data suggests that docetaxel plus prednisone seems to be the most effective treatment for men with mHRPC.

Cost-effectiveness

The results from the Assessment Group model suggest that treatment with docetaxel plus prednisone/prednisolone is cost-effective in patients with mHRPC as long as the health service is willing to pay £32,706 per additional QALY. Sensitivity analysis demonstrated the robustness of the estimate of cost-effectiveness to these variations.

Research Recommendations

- At the time of this assessment there were ongoing trials of docetaxel as the standard arm in combination with other therapies (described in section 4.1), therefore, until these trials are completed it is difficult to make any recommendations for further research of docetaxel.
- Future research should include the assessment of quality of life associated with different treatments including adverse events of treatment, using generic quality of life instruments, which are suitable for the purposes of cost-effectiveness analyses.

List of abbreviations

ASCO	American Society of Clinical Oncology
AUC	Area under the curve
BAUS	British Association of Urological Surgeons
CBA	Cost benefit analysis
CEA	Cost-effectiveness analysis
CI	Confidence interval
CEAC	Cost-effectiveness acceptability curve
CMA	Cost minimisation analysis
CR	Complete response
CUA	Cost utility analysis
ECOG	European Co-operative Oncology Group
EORTC	European Organization of Research and Treatment of Cancer
EVPI	Expected value of perfect information
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FDA	Food and Drug Administration
FLIC	Functional Living Index-Cancer
HR	Hazard ratio
HRPC	Hormone-refractory prostate cancer
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
i.v.	Intravenous
LASA	Linear analogue self-assessment
mHRPC	Metastatic hormone refractory prostate cancer
MRI	Magnetic resonance imaging
NA	Not applicable
NCI CTC	National Cancer Institute's Common Toxicity Criteria
NHS R&D HTA	NHS Research & Development Health Technology Assessment Programme
NICE	National Institute for Health and Clinical Excellence
Nd	Not determined
Ns	Not statistically significant
NS	Not stated
OR	Odds ratio
PP	Per protocol
PPI	Present Pain Intensity
PR	Partial response
PROSQOLI	Prostate Cancer-Specific Quality-of-life Instrument
PSA	Prostate Specific Antigen
RCT	Randomised controlled trial
QoL	Quality of life
QALY	Quality adjusted life year
RR	Relative risk
s.c.	Subcutaneous
SD	Standard deviation

Definitions of terms

Absolute risk reduction (ARR)	The difference between the event rates in the two groups, where the adverse event rate is less in the intervention group this suggests the intervention is beneficial.
Adverse effect/adverse event	An abnormal or harmful effect caused by, and attributable to, exposure to a chemical (e.g. a drug), which is indicated by some result such as death, a physical symptom or a visible illness. An event may be classified as adverse if it causes functional or anatomical damage, causes irreversible changes in the homeostasis of the organism or increases the susceptibility of the organism to other chemical or biological stress.
Alopecia	Baldness/the loss of body hair.
Anaemia	An abnormally low level of red blood cells in the blood. Red blood cells are responsible for carrying oxygen around the body.
Antineoplastic	Inhibiting or preventing the development of neoplasms, and checking the maturation and proliferation of malignant cells.
Arthralgia	Joint pain.
Asthenia	Weakness, lack of energy and strength.
Bias	Deviation of results or inferences from the truth, or processes leading to such deviation. Any trend in the collection, analysis, interpretation, publication or review of data that can lead to conclusions that are systematically different from the truth.
Blinding	A procedure used in clinical trials to avoid the possible bias that might be introduced if the patient and / or doctor knew which treatment the patient would be receiving. If neither the patient nor the doctor is aware of which treatment has been given, the trial is termed 'double-blind'. If only one of the patient or doctor is aware, the trial is called 'single-blind'.
Carcinoma	A cancerous growth.
Censored data	Censorship means that the event does not occur during the period of observation and the time of event is unknown, but these cases are incorporated into the analysis. Those whose event is unknown, or who are lost to the study (right censored) or new patients introduced into the study (left censored), add to the information on patients whose event time is known (uncensored) at each time interval.
Chemotherapy	The use of drugs that are capable of killing cancer cells, or preventing/slowing their growth.
Clodronate	Clodronate is a medicine used to treat a high level of

	calcium in the blood caused by changes in the body that happen with cancer. Clodronate also treats the weakening in the bones when cancer has spread to the bones from another part of the body.
Co-intervention	In a randomised controlled trial, the application of additional diagnostic of therapeutic procedures to members of either the experimental or reference group, or to both groups.
Complete response	The total disappearance of all detectable malignant disease for at least 4 weeks.
Confidence Interval (CI)	A measure of precision of statistical estimate.
Confounding	(1) The masking of an actual association or (2) false demonstration of an apparent association between the study variables when no real association between them exists.
Cost-benefit analysis	An attempt to give the consequences of the alternative interventions a monetary value. In this way, the consequences can be more easily compared with the costs of the intervention. This involves measuring individuals' "willingness to pay" for given outcomes, and can be difficult.
Cost-effectiveness analysis	The consequences of the alternatives are measured in natural units, such as years of life gained. The consequences are not given a monetary value.
Cost-effectiveness acceptability curve (CEAC)	A graphical representation of the probability of an intervention being cost effective over a range of monetary values for society's willingness to pay for an additional unit of health gain.
Cost-minimisation analysis	When two alternatives are found to have equal efficacy or outcomes (consequences). Therefore, the only difference between the two is cost. This is sometimes considered to be a sub-type of cost-effectiveness analysis.
Cost-utility analysis	The consequences of alternatives are measured in 'health state preferences', which are given a weighting score. In this type of analysis, different consequences are valued in comparison with each other, and the outcomes (e.g. life-years gained) are adjusted by the weighting assigned. In this way, an attempt is made to value the quality of life associated with the outcome so that life-years gained become quality-adjusted life-years gained.
Coumadin	An anticoagulant.
Cycle	Chemotherapy is usually administered at regular intervals. A cycle is a course of chemotherapy followed by a period in which the body recovers from the adverse events of the drug(s).
Cytotoxic	Toxic to cells. This term is used to describe drugs that kill cancer cells or slow their growth.

Dyspnoea	Difficult or labored breathing, shortness of breath.
ECOG performance status	0: fully active, able to carry on all pre-disease performance without restriction. 1: restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. 2: ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours. 3: capable of only limited self-care, confined to bed or chair more than 50% of waking hours. 4: completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair. 5: dead.
End-point	A clearly defined outcome or event associated with an individual in a medical investigation.
EORTC	The European Organization for Research and Treatment of Cancer (EORTC) is an organisation set up to conduct, develop, coordinate, and stimulate laboratory and clinical research in Europe to improve the management of cancer and related problems by increasing survival but also quality of life of patients.
Epistaxis	Nose bleed.
Evaluable disease	Unidimensionally measurable lesions, masses with margins not clearly defined, lesions with both diameters ≤0.5 cm, lesions on scan with either diameter smaller than the distance between cuts, palpable lesions with either diameter ≤ 2 cm; malignant ascites or pleural effusion in conjunction with serum levels of CA-125>100 U/mL in the absence of cirrhosis (CA-125 is a glycoprotein antigen expressed by some ovarian cancers).
External validity	The ability to generalise the results from a particular experiment to a larger population.
FACT-P	Quality of life questionnaire (Functional Assessment of Cancer Therapy-Prostate)
First-line therapy	The first chemotherapy regimen (usually administered with curative intent) given to patients who have been newly diagnosed with ovarian cancer, or who had an early stage of the disease which has been previously treated with surgery alone but has since relapsed and requires chemotherapy.
FLIC	Quality of life instrument (Functional Living Index-Cancer)
Forest plot	The way in which results from a meta-analysis are often presented. Results are displayed graphically as horizontal lines representing the 95% or 99% confidence intervals of the effect of each trial (strictly the 95% or 99% CIs of a relative risk of the

	intervention group compared with the control group).
Granulocytopenia	A marked decrease in the number of granulocytes.
Hazard ratio	Measure of relative risk used in survival studies.
Heterogeneous	Of differing origins or different types.
Histological grade	The degree of malignancy of a tumour as judged by histology.
Histological type	The type of tissue found in a tumour as determined by histology.
Histology	The examination of the cellular characteristics of a tissue.
Hormone-refractory	Progressive disease, evidenced by PSA rise or clinical progression, after first line hormonal therapy.
Incidence	The number of new events (new cases of a disease) in a defined population, within a specified period of time.
Incremental cost-effectiveness ratio	An expression of the additional cost of health gain associated with an intervention relative to an appropriate comparator. Expressed as the difference in mean costs (relative to the comparator) divided by the difference in mean effects. Sometimes expressed with confidence intervals.
Intention-to-treat analysis method	An analysis of a clinical trial where participants are analysed according to the group to which they were initially randomly allocated, regardless of whether or not they dropped out, fully complied with the treatment or crossed over and received the other treatment.
Interim analysis	A formal statistical term indicating an analysis of data part-way through a study.
Internal validity	The degree to which a study is logically sound and free of confounding variables.
Kaplan-Meier curves (also called product limit method)	A non-parametric method of compiling life or survival tables, developed by Kaplan and Meier in 1958. This combines calculated probabilities of survival and estimates to allow for censored observations, which are assumed to occur randomly. The intervals are defined as ending each time an event (e.g. death, withdrawal) occurs and are therefore unequal.
Karnofsky performance status scale	A performance measure for rating the ability of a person to perform usual activities, evaluating a patient's progress after a therapeutic procedure, and determining a patient's suitability for therapy. It is used most commonly in the prognosis of cancer therapy, usually after chemotherapy and customarily administered before and after therapy. A measure is given by a physician to a patients

	ability to perform certain ordinary tasks: 100 – normal, no complaints; 70 – unable to carry on normal activity; 50 – requires considerable assistance; 40 – disabled; 30 – hospitalisation recommended.
Localised disease	Disease that is confined to part of an organ or tissue.
Leucopenia	An abnormally low level of leucocytes in the blood. Leucocytes are white blood cells which help to fight infections within the body.
Lymph nodes	Small organs that act as filters in the lymphatic system. Lymph nodes close to a primary tumour are often the first sites to which a tumour spreads.
Measurable disease	The presence of lesion(s) that can be unidimensionally or bidimensionally measured by physical examination, echography, radiography or computed tomographic scan.
Meta-analysis	A quantitative method for combining the results of many studies into one set of conclusions.
Metastasis/metastatic cancer	Cancer that has spread to a site distant from the original site.
Mortality rate	The proportion of deaths in a population or in a specific number of the population per unit of time.
Myalgia	Muscle pain.
Neuropathy	A term to describe any disorder of the neurones or nerves of the body.
Neutropenia	An abnormally low level of neutrophils in the blood. Neutrophils belong to a group of white blood cells known as granulocytes, which are important in fighting infections within the body.
Number needed to treat (NNT)	In clinical treatment regimens, the number of patients with a specified condition who must follow the specified regimen for a prescribed period in order to prevent occurrence of specified complications or adverse outcomes of the condition. Mathematically equal to 1/ (risk difference).
Oedema	A build-up of excess fluid in the body tissues.
Palliative	Anything that serves to alleviate symptoms due to the underlying cancer but is not expected to act as a cure.
Paresthesia	Numbness/tingling or ‘pins and needles’ sensation of the skin.
Partial response	At least a 50% decrease in tumour size for more than 4 weeks without an increase in the size of any area of known malignant disease or the appearance of new lesions.
Phase II trial	A study with a small number of patients diagnosed with the disease for which the drug is being studied. In this study, the efficacy and safety of the new drug

	is tested.
Phase III trial	A study with a large number of patients diagnosed with the disease for which the drug is being studied and is unlicensed for the indication. In this study, the drug is tested against a placebo or alternative gold standard treatment.
Placebo	A 'dummy' treatment administered to the reference group in a controlled clinical trial in order to distinguish the specific and non-specific effects of the experimental treatment (i.e. the experimental treatment must produce better results than the placebo in order to be considered effective).
PPI	Present Pain Intensity scale from the McGill-Melzack questionnaire.
Prevalence	The measure of the proportion of people in a population who have some attribute or disease at a given point in time or during some time period.
Progressive disease	Used to describe a tumour that continues to grow or where a patient develops more metastatic sites.
Progression-free survival	The time from the start of study drug administration to documented disease progression or death due to any cause while the participant was on study drug or during the long-term follow-up period.
Prophylaxis/prophylactic treatment	An intervention (i.e. any act, procedure, drug or equipment) used to guard against or prevent an unwanted outcome.
Proportional hazards model	Regression method for modelling survival times. The outcome variable is whether or not the event of interest has occurred, and if so, after what period of time; if not, the duration of follow-up. The model predicts that hazard or risk of the event in question at any given time.
Prostate Specific Antigen	A substance produced by cells from the prostate. Under normal circumstances, PSA is secreted by the prostate into semen to help with reproduction by preventing the coagulation of semen. However, small amounts of PSA naturally leak out into the bloodstream as well. When prostate cancer is present, the prostate ducts that normally secrete PSA into the urethra get clogged and more PSA leaks out of the prostate into the bloodstream.
p-value	In the context of significant tests, the *p*-value represents the probability that a given difference is observed in a study sample, when such a difference does not exist in the relevant population. Small p-values indicate stronger evidence to reject the null hypothesis of no difference.
Quality-adjusted life-years (QALYs)	A measure of health care outcomes that adjusts gains (or losses) in years of life subsequent to a health care

	intervention by the quality of life during those years. QALYs can provide a common unit for comparing cost-utility across different interventions and health problems
Quality of Life (QoL)	A concept incorporating all the factors that might impact on an individual's life, including factors such as the absence of disease or infirmity as well as other factors which might affect their physical, mental and social well-being.
Quality of Life Questionnaire (QLQ-C30)	A self-administered quality of life questionnaire developed by the EORTC for the measurement of health-related quality of life. The questionnaire consists of nine scales – one global QOL scale, five function scales (physical, role, emotional, cognitive, and social), and three symptom scales (fatigue, pain, nausea/vomiting) and questions on six single items (dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea, and financial impact). Higher scores on the function scales indicate better functioning and QOL, whereas higher scores on the symptom scales indicate the presence of more symptoms.
Random allocation	A method of allocation to ensure that the treatment assignment is unpredictable.
Randomised controlled trial (RCT) (also randomised clinical trial)	These are designed to measure the efficacy and safety of particular types of healthcare interventions, by randomly assigning people to one of two or more treatment groups and, where possible, blinding them and the investigators to the treatment that they are receiving. The outcome of interest is then compared between the treatment groups. Such studies are designed to minimise the possibility of an association due to confounding and remove the many sources of bias present in other study designs.
Relative risk (RR)	Also called the 'risk ratio'. A common way of estimating the risk of experiencing a particular effect or result. A RR > 1 means a person is estimated to be at an increased risk, while a RR < 1 means a person is apparently at decreased risk. A RR of 1.0 means there is no apparent effect on risk at all, e.g., if the RR = 4.0, the result is about 4 times as likely to happen, and 0.4 means it is 4 times less likely to happen. The RR is expressed with confidence intervals: e.g., RR=3.0 (95% CI: 2.5, 3.8). This means the result is 3 times as likely to happen - anything from 2.5 times as likely, to 3.8 times as likely. It is statistically significant. On the other hand, RR=3.0 (95% CI: 0.5, 8.9), means it is also estimated to be 3 times as likely, but it is not

	statistically significant. The chances go from half as likely to happen (0.5 a decreased chance), to nearly 9 times as likely to happen (8.9 an increased chance).
Relative risk reduction (RRR)	Alternative way of expressing relative risk. It is calculated as follows: RRR= (1 – RR) x100% The RRR can be interpreted as the proportion of the initial or baseline "risk" which was eliminated by a given treatment or intervention, or by avoidance of exposure to a risk factor.
Recurrent disease	Disease that re-appears after a period during which it has shown no measurable/detectable signs.
Risk difference	The difference (absolute) in the proportion with the outcome between the treatment and control groups. If the outcome represents an adverse events and the risk difference is negative (below zero) this suggests that the treatment reduces the risk – referred to as the absolute risk reduction.
Salvage therapy	Any therapy given in the hope of getting a response when the "standard" therapy has failed. This may overlap with "second-line" therapy, but could also include therapy given for patients with refractory disease i.e. disease that has never responded to first-line therapy.
Second-line therapy	The second chemotherapy regimen administered either as a result of relapse after first-line therapy or immediately following on from first-line therapy in patients with progressive or stable disease. Depending on the circumstances patients may be treated with the same regimen again, or a different regimen. In either case this is defined as second-line therapy.
Stable disease	No change or less than a 25% change in measurable lesions for at least 4-8 weeks with no new lesions appearing.
Staging	The allocation of categories (e.g. for ovarian cancer FIGO stages I to IV) to tumours, defined by internationally agreed criteria. Tumour stage is an important determinant of treatment and prognosis.
Stomatitis	Inflammation/ulceration of the mouth.
Taxane naïve	Patients who had not received a taxane as part of first-line therapy.
Thrombocytopenia	An abnormally low level of platelets in the blood. Platelets play a role in the blood clotting process.
Time to progression	The length of time from the start of treatment (or time from randomisation within the context of a clinical trial) until tumour progression.
Utility	A measure of the strength of an individual's preference for a given health state or outcome. Utilities assign numerical values on a scale from 0

	(death) to 1 (optimal or 'perfect' health), and provide a single number that summarises health-related quality of life. Hence, utility has been described as a global measure of health-related quality of life. Sometimes 'utility' is only used to refer to preferences (on the 0-1 scale) that are elicited using methods which introduce risky scenarios to the respondent (standard gamble), with the term 'values' used to refer to other type of preferences.
Values	An alternative measure of the strength of an individual's preference for a given health state or outcome. In contrast to utilities, values reflect preferences elicited in a risk-less context.

1. Aim of the review

This review examined the clinical effectiveness and cost-effectiveness of docetaxel (Taxotere®, Sanofi-Aventis) in combination with prednisone/prednisolone versus other chemotherapy regimens, best supportive care (which may include radiotherapy, corticosteroids, oxygen, antibiotics and analgesics) or placebo.

The patient population that the review addressed was men with metastatic hormone-refractory prostate cancer (mHRPC).

2. Background

2.1. Description of underlying health problem

Epidemiology

Prostate cancer is the most common male cancer, excluding non-melanoma skin cancer, in the UK, accounting for around 13% of male cancer deaths. In 2001, there were 26,027 new cases in England and 1,746 in Wales, giving age standardised incidence rates of 89.8 and 92.6 per 100,000 men respectively.[1] In 2003 there were 8,582 deaths in England and 579 in Wales, giving age-standardised mortality rates of 27.3 and 28.6 per 100,000 men respectively.[2] The 5-year survival rate in the UK for prostate cancer was around 65% for patients diagnosed in the period 1996-1999.[3] Data on the epidemiology of mHRPC are limited.

Aetiology, pathology and prognosis

The primary risk factor for prostate cancer is increasing age, with 90% of all cases occurring in men over 60 and 42% in men over 75.[4] The highest worldwide rates are observed in Afro-American men, with much lower rates seen in men of Asian origin. It is likely that multi-factorial environmental and genetic factors are implicated. Diets high in animal fats and dairy products appear to be associated with increased risk.[5] As prostate cancer does not occur in castrated men, the male sex hormone testosterone is thought to be implicated in prostate cancer aetiology. High levels of insulin-like growth factor (IGF-1) a protein involved in cell metabolism may also be involved.[6] About 9% of cases are thought to have a genetic component, which is particularly

important in cases developing at an early age; around 40% of cases in men under 55 years may have a genetic predisposition.[7]

The extent of prostate cancer is classified into stages I - IV. At stages I and II the disease is confined to the prostate. At stage III the tumour is more locally advanced and at stage IV it is either locally advanced and invading local adjacent structures, or has associated distant metastases. Approximately 22% of cases will be diagnosed at stage IV,[8] with an additional 25% of patients developing metastases throughout the course of the disease.[9] The most important prognostic factor is the growth pattern or grade of the tumour, assessed using the Gleason scoring system. Gleason scores range from <4 for less aggressive to 8-10 for more aggressive tumours. Other important prognostic factors are prostate specific antigen (PSA) level and the extent of local tumour spread.[8]

Significance in terms of ill-health

Prostate cancer was responsible for 39,283 hospital episodes in 2003-4.[4] Although incidence rates have increased, mortality from the disease has remained largely unchanged. Survival rates have been improving for the last two decades, partly due to the impact of detecting clinically unapparent, more slowly growing tumours as a result of more widespread PSA screening.[10] With an increased ageing population, there will be further increases in the rate of diagnosis.[11] The lifetime risk for being diagnosed with prostate cancer is 1 in 13.[1]

Hormone-refractory prostate cancer

The majority of prostate cancers initially respond to hormone therapy. The median response duration to first-line hormonal therapy in metastatic disease is around 18 months.[12] However, in the majority of patients the cancer will become resistant to hormonal treatment and will progress to mHRPC. mHRPC is defined as either biochemically or clinically progressive metastatic disease despite castrate serum levels of testosterone.[9] At this stage of the disease, the prognosis is poor, and survival is not expected to exceed between 9 and 12 months.[13] Prior to the licensing of docetaxel for the treatment of mHRPC, treatment was generally aimed at symptom control. While pain reduction and improvements in quality of life were achieved in

substantial proportions of patients (up to 80%), survival did not appear to be prolonged.[13] However preliminary results show that it is possible that docetaxel may also help to improve overall survival for patients with mHRPC.[9]

2.2. Current service provision

There is no current agreement about a gold standard treatment for mHRPC in the UK. Options include second-line hormonal therapy, chemotherapy with or without corticosteroids and best supportive care, dependent on the symptoms, site of relapse, performance status of the patient and presence of other co-morbidities.[9] Best supportive care can be provided with radiotherapy, bisphosphonates, steroids and analgesics and is the only option for patients who are too ill to tolerate further active intervention. Treatment in this setting is aimed at improvement of symptoms and control rather than cure.[8]

Current advice from NICE states that chemotherapy should be considered and trials of chemotherapy supported, while palliative radiotherapy should also be considered as a treatment option.[8] The use of chemotherapy in mHRPC in the UK is widespread and likely to increase (personal communication M Mason).

2.3. Description of new intervention

Docetaxel is a member of a class of drugs known as taxanes, derived from precursor extracted from the needles of the European yew tree, *Taxus baccata*.[14] Docetaxel is a mitotic inhibitor, which acts by disrupting the microtubular network that is essential for mitotic and interphase cellular functions. It promotes the assembly of tubulin into stable microtubules and inhibits microtubule depolymerisation, causing inhibition of cell division and cell death.[15]

Docetaxel

The following section of the report summarises the product characteristics for docetaxel, available from the electronic Medicine Compendium[16] (www.medicines.org.uk/).

Docetaxel (Taxotere®, Sanofi-Aventis) is available as a 20 mg or 80 mg concentrate and solvent for solution for infusion. Docetaxel is licensed for use in combination with prednisone or prednisolone for the treatment of patients with mHRPC. Prednisone is not used in the UK, but it is reasonable to use docetaxel plus prednisone data in this review of docetaxel plus prednisolone. Docetaxel is administered as a one-hour infusion once every three weeks. The recommended dose is 75 mg/m^2, while prednisone/prednisolone should be administered continuously, at a dose of 5 mg orally twice a day. Safety and efficacy have not been established for children, and there are no special instructions for the use of docetaxel in the elderly.

New guidelines prepared by the British Association of Urological Surgeons (BAUS) propose considering the use of docetaxel, for symptomatic patients who are fit for chemotherapy.[17] It is acknowledged that the clinical management of mHRPC is multimodal rather than sequential and at any given time a patient may receive a combination of palliative treatments.

Contraindications

- Hypersensitivity to the active substance or any component of the medicinal product.
- Baseline neutrophil count of <1,500 cells/mm^3.
- Severe liver impairment.
- Use of other medicinal products, when combined with docetaxel.

Special warnings and special precautions for use

- Pre-medication with 8 mg of oral dexamethasone, 12 hours, 3 hours and 1 hour prior to the docetaxel infusion, can reduce the incidence and severity of fluid retention and hypersensitivity reactions.
- Neutropenia is the most frequent adverse reaction to docetaxel, and thus frequent monitoring of complete blood counts should be undertaken. Patients can be retreated with docetaxel when neutrophils recover to ≥1,500 cells/mm^3. In cases of severe neutropenia, defined as neutrophils of <500 cells/mm^3 for seven days or more, a reduction in dose of docetaxel is recommended.

- Patients should be observed closely for hypersensitivity reactions, particularly during the first and second infusions. These reactions may occur within a few minutes of beginning the docetaxel infusion, and thus facilities for the treatment of hypotension and bronchospasm should be readily available.
- Minor hypersensitivity reactions, such as flushing or localised cutaneous reactions, do not require therapy interruption. More severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of docetaxel therapy. Those patients that have experienced severe hypersensitivity reactions should not be re-challenged with docetaxel.
- Localised skin erythema of the palms of the hands and soles of the feet with oedema followed by desquamation has been observed. Severe symptoms such as eruptions followed by desquamation leading to the interruption or discontinuation of docetaxel therapy were reported.
- Patients with severe fluid retention, such as pleural effusion, pericardial effusion and ascites should be monitored closely.
- No data are available in patients with hepatic impairment treated by docetaxel in combination.
- No data are available in patients with severely impaired renal function.
- The development of severe peripheral neurotoxicity requires a reduction of dose.

Adverse events

- Severe neutropenia is very common, but is reversible and not cumulative.
- Non-haematological adverse events occurring in more than 5% of patients include alopecia, nail changes, fluid retention, nausea, diarrhoea, stomatitis/pharyngitis, taste disturbance, vomiting, sensory neuropathy, anorexia, tearing, myalgia and fatigue.

Anticipated costs

The cost of docetaxel concentrate for intravenous infusion is £162.75 for a 0.5mL vial and £534.75 for a 2 mL vial (both with diluent). [18] Therefore the cost of docetaxel at 75 mg/m^2 at three weekly intervals for up to 10 cycles is £11,000.[19]

2.4. Comparator/alternative technologies

The Food and Drug Administration (FDA) approved the use of mitoxantrone (Novantrone®, Wyeth) plus prednisone as the standard treatment for mHRPC in the USA in 1996.[20] In the USA, along with many other western countries, mitoxantrone is considered to be one of the most effective palliative treatments for mHRPC. Estramustine (Estracyt®, Pfizer) is an effective treatment for mHRPC, although it is poorly tolerated compared with mitoxantrone, especially by the elderly, and is therefore not widely used.[11] For those patients unable to tolerate chemotherapy best supportive care is offered. The use of corticosteroids is the only form of best supportive care for which evidence was identified for this review. The properties of mitoxantrone and estramustine are described below.

Mitoxantrone

Mitoxantrone is licensed in the UK, but not for mHRPC, although it is widely used in the UK for mHRPC patients who are fit for chemotherapy (personal communication M Mason).

The following section of the report summarises the product characteristics for mitoxantrone, (Novantrone®, Wyeth) available from drug information online.[21] (http://www.drugs.com/pdr/mitoxantrone_hydrochloride.html).

Mitoxantrone is an anthracenedione, with a relatively modest toxicity profile apart from myelosuppression and dose-related cardiotoxicity.[9] It is a DNA-reactive agent that intercalates into DNA causing crosslinks and strand breaks, it also interferes with RNA and can inhibit the enzymes responsible for uncoiling and repairing damaged DNA.

Mitoxantrone is available as a 20 mg, 25 mg or 30 mg concentrate for injection. Mitoxantrone in combination with corticosteroids is indicated as initial chemotherapy for the treatment of patients with pain related to advanced HRPC in the USA. The recommended dosage of mitoxantrone is 12 to 14 mg/m^2 given as a short intravenous infusion every 21 days. Safety and efficacy in children has not been established and

there are no special instructions for the use of mitoxantrone in the elderly; however the greater sensitivity of some older individuals has not been ruled out.

Contraindications

- Hypersensitivity to the active substance.
- Baseline neutrophil count of <1,500 cells/mm^3

Special warnings and special precautions for use

- Myocardial toxicity may occur during or after therapy with mitoxantrone, so patients should be monitored for evidence of cardiac toxicity and questioned about symptoms of heart failure prior to initiation of treatment.
- Cardiac toxicity may be more common in patients with prior treatment with anthracyclines, prior mediastinal radiotherapy, or with pre-existing cardiac disease. Such patients should have regular monitoring from the initiation of mitoxantrone treatment.
- Mitoxantrone clearance is reduced by hepatic impairment, therefore patients with hepatic impairment should be treated with caution and dosage adjustment may be required.
- Complete blood counts should be obtained prior to each course of mitoxantrone, accompanied by close and frequent monitoring of haematological and chemical laboratory parameters, as well as frequent patient observation.
- Patients with pre-existing myelosuppression should not receive mitoxantrone unless the possible benefit from such treatment warrants the risk of further medullary suppression.
- No data are available in patients with renal impairment.
- No data are available in patients treated by mitoxantrone concomitantly with other medications.

Adverse events

- No non-haematologic adverse events of grade 3 or 4 were seen in more than 5% of patients.

- Severe neutropenia is very common, as is mild to moderate nausea and vomiting.
- Congestive heart failure, tachycardia, arrythmias, chest pain and asymptomatic decreases in left ventricular ejection fraction have been reported.

Estramustine

The following section of the report summarises the product characteristics for estramustine, (Estracyt®, Pfizer) available from the Electronic Medicine Compendium.[22] (www.medicines.org.uk/)

Estramustine is a chemical compound consisting of oestradiol and nitrogen mustard, that has mild anti-microtubule actions. It has a dual mode of action; it acts as an anti-mitotic agent and exerts an anti-gonadotrophic effect. Estramustine also binds to a protein present at the tumour site, resulting in an accumulation of the drug at the target site.

Estramustine is available in 140 mg gelatine capsules. Estramustine is licensed in the UK for the treatment of carcinoma of the prostate, especially in cases unresponsive to, or relapsing after, treatment by hormones. The dosage of estramustine can range from one to ten capsules per day, with standard starting doses of four to six capsules per day. Each capsule should be taken orally, not less than one hour before or two hours after meals. The capsules should not be taken with milk or milk products. Estramustine should not be administered to children.

Contraindications

- Hypersensitivity to oestradiol or nitrogen mustard.
- Children.
- Peptic ulceration, severe liver dysfunction or myocardial insufficiency.

Special warnings and precautions for use

- Caution should be taken if using in patients with moderate to severe bone marrow depression, thrombophlebitis, thrombosis, thromboembolic disorders, cardiovascular disease, coronary artery disease and congestive heart failure.

- Caution should also be exercised in patients with diabetes, hypertension, epilepsy, hepatic and renal impairment and diseases associated with hypercalcaemia.
- Blood counts, liver function tests and serum calcium in hypercalcaemia should be performed at regular intervals, and calcium levels closely monitored.
- Milk, milk products or any drugs containing calcium may impair the absorption of estramustine and should not be taken concomitantly.

Adverse events

- The most common adverse events are gynaecomastia and impotence, anaemia, granulocytopenia, nausea and vomiting (particularly during the first two weeks of treatment), and fluid retention and oedema.
- The most serious adverse events are thromboembolism, ischaemic heart disease and congestive heart failure.
- Therapy with estramustine should be discontinued immediately should angioneurotic oedema occur.

3. Methods for literature review of effectiveness and cost-effectiveness

3.1. Search strategy

As stated in Chapter 1, the aim of this review was to assess the clinical and cost-effectiveness of docetaxel plus prednisone/prednisolone versus other chemotherapy regimens, best supportive care or placebo. A scoping search was conducted which identified a study of docetaxel plus prednisone versus mitoxantrone plus prednisone. The scoping search, however, did not identify any trials comparing docetaxel plus prednisone/prednisolone with any of the other relevant treatments. Trials comparing mitoxantrone (Novantrone®, Wyeth) with other chemotherapies and corticosteroids (used as best supportive care) were identified. Therefore, in order to allow for a comparison between docetaxel and other relevant treatments, the clinical effectiveness and cost-effectiveness of mitoxantrone, the common comparator to these other treatments, was also reviewed.

Sources

Searches were undertaken on the following databases to identify relevant clinical and cost-effectiveness literature. Full details of the search strategies are reported in Appendix 10.1.

- Ovid MEDLINE and Ovid MEDLINE In Process And Other Non-Indexed Citations (Ovid Online – www.ovid.com)
- EMBASE (Ovid Online – www.ovid.com)
- Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library on cd-rom)
- The Cochrane Database of Systematic Reviews (CDSR) (The Cochrane Library on cd-rom)
- National Research Register (NRR) (cd-rom)
- Health Technology Assessment Database (HTA) (CRD administration database)
- NHS Economic Evaluation Database (NHS EED) (CRD administration database)
- Database of Abstracts of Reviews of Effects (DARE) (CRD administration database)

- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (Ovid Online – www.ovid.com)
- Health Management Information Consortium (HMIC) (Ovid Online – www.ovid.com)
- ISI Science and Technology Proceedings (Internet - Web of Knowledge - http://wos.mimas.ac.uk/)
- Social Science Citation Index (Internet - Web of Knowledge - http://wos.mimas.ac.uk/)
- Index to Theses (Internet - http://www.theses.com/)
- SIGLE (SilverPlatter ARC2 – http://www.ovid.com)
- Inside Conferences (DialogLink - http://www.dialog.com/)
- BIOSIS Previews (DialogLink - http://www.dialog.com/)
- Current Controlled Trials (Internet - http://controlled-trials.com/)
- ClinicalTrials.gov (Internet - http://clinicaltrials.gov/)

Searches were also undertaken on several Internet resources.

- International Cancer Research Portfolio (ICRP) (Internet - http://www.cancerportfolio.org/)
- National Cancer Institute Clinical Trials PDQ (Internet http://www.cancer.gov/Search/SearchClinicalTrialsAdvanced.aspx)
- American Society of Clinical Oncology (Internet - http://www.asco.org)

Terminology

The terms for the search strategies were identified through discussion between an information officer and the rest of the research team, by scanning the background literature, and by browsing the MEDLINE thesaurus (MeSH). All databases were searched from their inception to the date of the search. Searches took place during April 2005 (see Appendix 10.1 for dates of individual searches). No language or other restrictions were applied.

Management of references

As several databases were searched, some degree of duplication resulted. In order to manage this issue, the titles and abstracts of bibliographic records were downloaded and imported into Endnote bibliographic management software to allow for the removal of duplicate records.

Handsearching

The bibliographies of all included studies, the industry submission and papers retrieved for background information were reviewed to identify further relevant studies.

Results

The literature searches retrieved 1065 references. All references were managed using Endnote software version 6. The full details of the search strategies are given in Appendix 10.1.

3.2. Inclusion and exclusion criteria

Two reviewers independently screened all titles and abstracts. Full paper manuscripts of any titles/abstracts that were considered relevant by either reviewer were obtained where possible. The relevance of each study was assessed according to the criteria set out below. Studies that did not meet all the criteria were excluded and their bibliographic details listed with reasons for exclusion in Appendix 10.2. Any discrepancies were resolved by consensus and if necessary a third reviewer was consulted.

Interventions

This review covered the effectiveness of the following two alternative chemotherapeutic agents:

- Docetaxel (Taxotere®, Sanofi-Aventis) in combination with prednisone/prednisolone, which is within its licensed indication.
- Mitoxantrone (Novantrone®, Wyeth) in combination with a corticosteroid, which is not licensed for use in this patient group in the UK. Mitoxantrone is licensed in combination with corticosteroids for mHRPC in the USA. In order

to be inclusive we assessed mitoxantrone in combination with any form of corticosteroid, since it is not licensed for mHRPC in the UK, its use is not restricted to be in combination with prednisone/prednisolone.

Comparators

The comparators that were considered included any chemotherapy regimen, best supportive care (which may include radiotherapy, corticosteroids, oxygen, antibiotics and analgesics) or placebo.

Participants

Men with metastatic hormone-refractory prostate cancer (mHRPC).

Study design

Randomised controlled trials that compared docetaxel in combination with prednisone/prednisolone or mitoxantrone in combination with a corticosteroid with any chemotherapy regimen, best supportive care (which may include radiotherapy, corticosteroids, oxygen, antibiotics and analgesics) or placebo.

For the assessment of cost-effectiveness a broader range of studies were considered including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compared two or more options and considered both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analysis) were included.

Outcomes

Data on the following outcomes were included:

- Overall survival.
- Progression-free survival.
- Response rate (including complete and partial response).
- PSA decline.
- Adverse effects of treatment.
- Pain.
- Health-related quality of life.

- Costs from all reported perspectives.

Publication

A full English language paper copy or trial report of the study had to be available for it to be included in the review. Studies which were reported in abstract form only, and where no further information was available, were excluded. Descriptions of these studies are provided in Appendix 10.3. Foreign language papers were also excluded.

3.3. Data extraction strategy

Data relating to both study design and quality were extracted by one reviewer and independently checked for accuracy by a second. Disagreements were resolved through consensus and if necessary a third reviewer was consulted. Where multiple publications of the same study were identified, data were extracted and reported as a single study.

3.4. Quality assessment strategy

The quality of the individual studies was assessed by one reviewer and independently checked by a second. Disagreements were resolved through consensus, and if necessary a third reviewer was consulted. The quality of the clinical effectiveness studies was assessed according to criteria based on CRD Report No. 4.[23] The quality of the cost-effectiveness studies was assessed according to a checklist updated from that developed by Drummond et al.[24] This checklist reflects the criteria for economic evaluation detailed in the methodological guidance developed by NICE. Full details of the quality assessment strategy are reported in Appendix 10.4.

3.5. Methods of analysis/synthesis

3.5.1. Clinical effectiveness

Full data extraction and quality assessment have been presented for each individual study of clinical effectiveness. The possible effects of study quality on the effectiveness data and review findings are discussed. Data are reported separately for each outcome measure.

Where sufficient data were available, treatment effects are presented in the form of relative risks (RR) or hazard ratios (HR), as appropriate, together with corresponding 95% confidence intervals (CI). Time to event data (survival data) are presented as hazard ratios, which were estimated from number of events and log-rank p-value or survival curves where necessary, as described by Parmar et al.[25] Where relative risk estimates and corresponding 95% confidence intervals were not presented in the original trial report they have been calculated, using the numbers of events relative to the numbers analysed. The numbers analysed for individual outcomes were conservatively assumed to be equivalent to the numbers randomised to receive treatment if this information was not reported. In some cases the data are also presented in the form of Forest plots.

Two reviewers independently extracted the necessary information and performed all calculations of hazard ratios and relative risks to reduce the possibility of error. Appendix 10.5 shows an example of these calculations.

Data on response rate, health-related quality of life and pain were not collected consistently by trialists. The use of different definitions of response and different measurement scales precludes the statistical synthesis of these data.

Data on the following adverse events were collected: haematological toxicity including anaemia, thrombocytopenia, granulocytopenia, neutropenia, leucopenia, and non-haematological toxicity including nausea, vomiting, diarrhoea, stomatitis, myalgia, cardiac toxicity, pulmonary toxicity, arthralgia, dyspnoea, impaired left ventricular ejection fraction, shortness of breath, thrombosis, asthenia, headache, peripheral oedema, epistaxis, bone pain, sensory or motor neuropathy, anorexia, weight gain, change in taste, tearing, fatigue, allergic reactions, fluid retention, alopecia, nail and skin toxicities, and any other adverse events judged to be appropriate, such as infection associated reactions. The most commonly occurring adverse events are presented, where possible, along with details of grade 3 or 4 adverse events.

The small number of studies prevented the assessment of publication bias using funnel plots or the Egger test.[26] However, the risk is likely to be low, considering the attempts to locate unpublished data.

3.5.2. Cost-effectiveness

For the cost-effectiveness section of the report, details of each identified published economic evaluation, together with a critical appraisal of its quality are presented in structured tables. This included studies based on patient-level data and decision models and included any studies provided by the manufacturers.

For analysis based on patient-level data, the validity of the studies was assessed in terms of the sources of resource use and effectiveness data, the valuation methods used to cost the resource use and value patient benefits, the methods of analysis and the generalisability of results. For analysis based on decision models, the critical appraisal was based on a range of questions including:

i Structure of model.
ii Time horizon.
iii Details of key input parameters and their sources.
iv Methods of analysis (e.g. handling uncertainty).

3.5.3. Handling the company submissions

No data additional to the publications identified from the literature searches were presented in the company submissions in terms of clinical effectiveness, other than mean survival data calculated for one of the included studies (TAX 327).

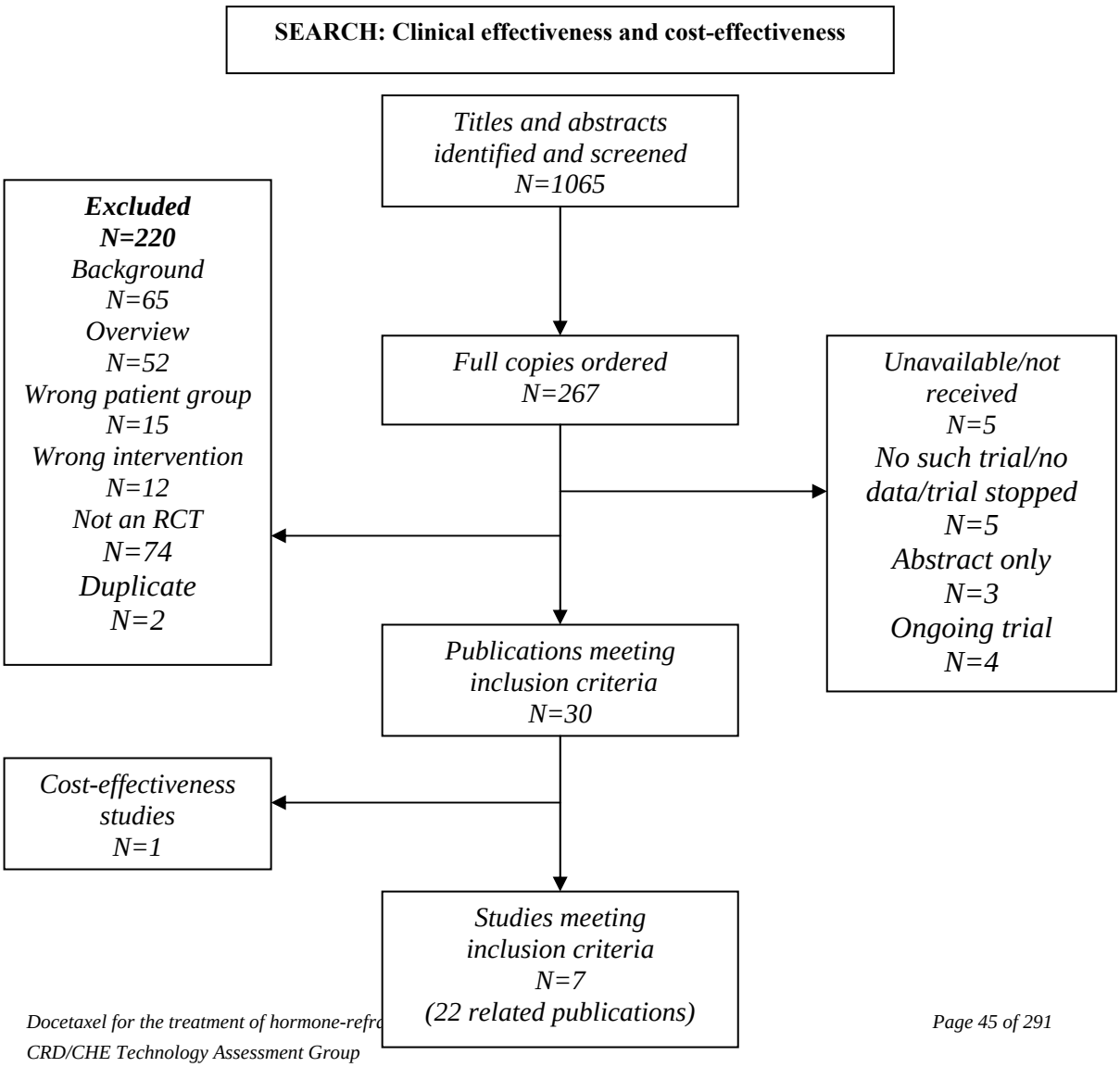
The economic evaluations included in the company submission were assessed. This included a detailed analysis of the appropriateness of the parametric and structural assumptions involved in the model included in the submission and an assessment of how robust the model was to changes in key assumptions. Following this analysis, a new model was developed to address some of the main issues identified in the review of cost-effectiveness evidence.

4. Results

4.1. Quantity of research available

A total of 1065 titles and abstracts were screened for inclusion in the review of clinical and cost-effectiveness. Of the titles and abstracts screened, 267 records were ordered as full papers. Seventeen records were not received/unavailable at the time of the assessment; five were not received in time/unavailable, three were not published because the trial was stopped prematurely (one record) or the study had negative results (two records relating to one trial), for two records the trialist did not recognise the trial, three records were only available in abstract form and four records related to ongoing trials. 250 full papers were assessed in detail. The process of study selection is shown in Figure 1.

Figure 1. Process of study selection for clinical and cost-effectiveness



For the assessment of the clinical effectiveness of docetaxel in combination with prednisone/prednisolone or mitoxantrone in combination with a corticosteroid for the treatment of hormone-refractory metastatic prostate cancer, seven RCTs were identified.

One of these RCTs used two schedules of docetaxel in combination with prednisone; one at the recommended dosage within its license (75 mg/m^2 every three weeks):

- Docetaxel plus prednisone versus mitoxantrone plus prednisone for the treatment of mHRPC.[27]

One RCT used docetaxel at two different dosages in combination with estramustine and prednisone:

- Doctaxel plus prednisone plus estramustine versus mitoxantrone plus prednisone for the treatment of mHRPC.[28]

One RCT used docetaxel with estramustine, but without prednisone/prednisolone:

- Docetaxel plus estramustine versus mitoxantrone plus prednisone for the treatment of mHRPC.[29]

Four trials used mitoxantrone, which is licensed in the UK, but not for patients with mHRPC. These trials were:

- Mitoxantrone plus prednisone versus prednisone alone for the treatment of mHRPC.[30, 31]
- Mitoxantrone plus hydrocortisone versus hydrocortisone alone for the treatment of mHRPC.[32]
- Mitoxantrone plus prednisone plus clodronate versus mitoxantrone plus prednisone plus placebo for the treatment of mHRPC.[33] Clodronate is a medicine used to treat a high level of calcium in the blood caused by changes in the body that happen with cancer. Clodronate also treats the weakening in the bones when cancer has spread to the bones from another part of the body.

A summary of the seven included RCTs is presented in Table 1 and full data extraction tables are presented in Appendix 10.6.

Table 1. Summary of included RCTs

Study	Study design	Participants	Intervention
TAX 327 (Sanofi-Aventis) Tannock et al. (2004)[27] Dagher et al. (2004)[34] Eisenberger et al. (2004)[35] Eisenberger et al. (2004) [36] Centre for Drug Evaluation and Research (2004)[37]	Phase III, multi-centre, stratified open-label RCT.	1,006 men with metastatic prostate cancer, with disease progression during hormonal therapy. Patients were required to have stable levels of pain for at least 7 days before randomisation.	Docetaxel (75 mg/m^2 on day 1 every 21 days) + prednisone or prednisolone (5 mg orally twice daily from day 1) versus docetaxel (30 mg/m^2 on days 1, 8, 15, 22 and 29 in a 6-week cycle) + prednisone or prednisolone (5 mg orally twice daily from day 1) versus mitoxantrone (12 mg/m^2 on day 1 every 21 days) + prednisone or prednisolone (5 mg orally twice daily from day 1).
Oudard et al. (2005)[28] Oudard et al. (2002)[38] Oudard et al.[39] Oudard et al. (2003)[40]	Phase II multi-centre, stratified open-label RCT.	130 men with metastatic prostate cancer, with disease progression despite androgen deprivation.	Docetaxel (70 mg/m^2 on day 2 every 21 days) + estramustine (840 mg in 3 divided doses on days 1 to 5 and 8 to 12) + prednisone (10 mg daily) versus docetaxel (35 mg/m^2 on days 2 and 9 every 21 days) + estramustine (840 mg in 3 divided doses on days 1 to 5 and 8 to 12) + prednisone (10 mg daily) versus mitoxantrone (12 mg/m^2 on day 1 every 21 days) + prednisone (10 mg daily).
SWOG 9916 Petrylak et al. (2004a)[29] Petrylak et al. (2004b)[41] Southwest Oncology Group [42] Berry et al. (2004)[43]	Phase III multi-centre, stratified open-label RCT.	770 men with metastatic prostate cancer, with disease progression despite androgen-ablative therapy and cessation of anti-androgen treatment.	Docetaxel (60-70 mg/m^2 on day 2 every 21 days) + estramustine (three times daily on days 1-5) versus mitoxantrone (12-14 mg/m^2 on day 1 every 21 days) + prednisone (5 mg twice daily).
Berry et al. (2002)[30] Gregurich et al.[44]	Phase III multi-centre, open-label RCT.	120 men with asymptomatic prostate cancer that had progressed on at least one hormonal regimen. 86% intervention group and 79% control group had bone metastases, 18% in both groups had lymph metastases.	Mitoxantrone (12 mg/m^2 every 21 days) + prednisone (5 mg orally twice daily) versus prednisone (5 mg orally twice daily).
CCI-NOV22 (Lederle Laboratories) Tannock et al. (1996)[31] Dowling et al. (2001)[45] Osoba et al. (1999)[46] Tannock et al. (1995)[47] Stockler et al. (1998)[48] Moore et al. (1996)[49] Dowling et al. (1998)[50] Center for Drug Evaluation and Research (1996)[20]	Phase III multi-centre, stratified open-label RCT.	161 men with metastatic prostate cancer, with disease progression despite standard hormonal therapy. Patients were required to have symptoms of pain.	Mitoxantrone (12 mg/m^2 every 21 days) + prednisone (5 mg orally twice daily) versus prednisone (5 mg orally twice daily).
CALGB 9182	Phase III	242 men with metastatic prostate cancer.	Mitoxantrone (14 mg/m^2 every 21 days) + hydrocortisone

Kantoff et al. (1999)[32] Kantoff et al. (1996)[51] Center for Drug Evaluation and Research (1996)[20]	multi-centre, stratified open-label RCT.	Antiandrogen withdrawal and disease progression were required before trial entry.	(30 mg orally in the morning, 10 mg orally in the evening) versus hydrocortisone (30 mg orally in the morning, 10 mg orally in the evening).
Ernst et al. (2003)[33] Anonymous (2001)[52] Ernst et al. (2002)[53]	Phase III multi-centre, stratified double blind RCT.	227 men with metastatic prostate cancer, with progressive bone disease despite castrate levels of testosterone. Patients were required to have stable levels of analgesic use for at least 7 days before randomisation.	Mitoxantrone (12 mg/m^2 every 21 days) + prednisone (5 mg twice daily) + clodronate (1,500 mg over 3 hours every 21 days) versus mitoxantrone (12 mg/m^2 every 21 days) + prednisone (5 mg twice daily) + placebo (1,500 mg saline over 3 hours every 21 days).

Relevant studies reported in abstract form only

In addition to the seven included trials for which there was a full publication available, a further two RCTs were identified that were reported in abstract form only. No further details of the studies were obtainable from the trialists and therefore the trials were excluded from the review. The interventions that were assessed in these trials were:

- Docetaxel plus estramustine versus docetaxel; Eymard et al. (2004)[54]
- Docetaxel versus docetaxel plus thalidomide; Salimichokami (2003)[55]

These trials are described in Appendix 10.3.

Systematic reviews/meta-analyses

One systematic review was identified, but was only reported in abstract form. No further details of the review were obtainable from the reviewers. The review assessed:

- Chemotherapy efficacy from controlled trials in HRPC patients; Casciano (2001)[56]

Ongoing studies

Four ongoing studies were identified. No further details of the studies were obtainable from the trialists. The interventions that were assessed in these trials were:

- Docetaxel plus prednisone plus placebo versus docetaxel plus prednisone plus bevacizumab; Anonymous (2005)[57]
- Docetaxel plus prednisone versus GVAX® prostate cancer vaccine; Cell Genesys[58]
- Docetaxel plus prednisolone versus docetaxel plus prednisolone plus zoledronic acid versus docetaxel plus prednisolone plus or minus zoledronic acid plus strontium-89 (Trapeze trial); James[59]
- Mitoxantrone versus paclitaxel plus carboplatin; Cabrespine (2005)[60]

Excluded studies

A total of 220 records were excluded as they did not meet the inclusion criteria for the review. However, of these, 65 papers were used as background articles for the review. The majority of the other excluded articles were non-systematic reviews and

commentaries or non-randomised studies. A full list of the excluded studies with the reasons for exclusion is presented in Appendix 10.2.

4.2. Description of included studies

The following section of the report provides a summary of the seven included RCTs. For each included study a summary of the trial has been provided followed by a description of the trial quality and the results of the trial. Table 2 summarises the pattern of comparisons for the seven included RCTs.

Table 2. Treatment comparisons

	Treatment comparisons					
Trial	D+P *	D+P+E*	D+E	M+C	M+C+Clo	C
TAX 327	✓			✓(M+P)		
Oudard et al.		✓		✓(M+P)		
SWOG 9916			✓	✓(M+P)		
Berry et al.				✓(M+P)		✓(P)
CCI-NOV22				✓(M+P)		✓(P)
CALGB 9182				✓(M+H)		✓(H)
Ernst et al.				✓(M+P)	✓	

*Evaluated at two different dosages
D=Docetaxel, P=Prednisone/Prednisolone, E=Estramustine, M=Mitoxantrone, C=Corticosteroid (either Prednisone or Hydrocortisone), Clo=Clodronate, H=Hydrocortisone.

From the table it can be seen that there are no head-to-head comparisons of docetaxel versus best supportive care (corticosteroids). However, all trials include a comparison with mitoxantrone plus a corticosteroid. Therefore, indirect comparisons using mitoxantrone plus a corticosteroid as a common comparator can be used to estimate the relative effectiveness of docetaxel versus best supportive care.

The following sections describe the results of each individual study. Following this we attempt to synthesise these data using narrative and formal quantitative approaches.

4.3. Clinical evidence

4.3.1. Docetaxel plus prednisone versus mitoxantrone plus prednisone

One RCT (TAX 327) was identified which aimed to determine whether docetaxel plus prednisone improves overall survival compared to mitoxantrone plus prednisone in men with advanced mHRPC. In addition to the main publication of the trial,[27] there were two abstracts,[35, 36] an approval package[37] and an approval summary[34] from the Center for Drug Evaluation and Research at the United States Food and Drug Administration. A further report was obtained from Sanofi-Aventis as part of the industry submission.[61]

Description of the trial comparing docetaxel plus prednisone with mitoxantrone plus prednisone

This multi-centre RCT included 1,006 men with mHRPC; 335 patients were randomised to receive a 1-hour i.v. infusion of docetaxel (75 mg/m^2 on day 1 every 21 days) plus oral prednisone (or prednisolone), herein referred to as the 3-weekly docetaxel group, 334 patients were randomised to receive a 30-minute i.v. infusion of docetaxel (30 mg/m^2 on days 1, 8, 15, 22 and 29 in a 6-week cycle) plus oral prednisone (or prednisolone), herein referred to as the weekly docetaxel group and 337 patients were randomised to receive a 30-minute i.v. infusion of mitoxantrone (12 mg/m^2 on day 1 every 21 days) plus oral prednisone (or prednisolone), herein referred to as the mitoxantrone group. Patients in the docetaxel groups also received pre-medication with dexamethasone. Patients were stratified by baseline pain level and Karnofsky performance-status score. The baseline characteristics of patients across the three groups appear to have been well balanced in terms of Gleason score, PSA level, presence of pain, performance status, evidence of progression at entry (bone scan, increase in lesions or PSA), previous treatments, age, extent of disease, race and stage of disease at diagnosis.

For inclusion in the trial patients had to have clinical or radiological evidence of metastatic disease with disease progression during hormonal therapy; an increase in serum PSA level on three consecutive measurements obtained at least one week apart, or evidence from physical examination or imaging studies. Patients were also required to have a Karnofsky performance-status score of at least 60%, and stable

levels of pain for at least seven days before randomisation; daily variation of no more than one in Present Pain Intensity (PPI) scale from the McGill-Melzack questionnaire or 25% in analgesic score.

The median number of cycles received by the 3-weekly docetaxel group was 9.5 (range 1-11), the median number received by the group receiving weekly docetaxel (6-week cycle) was 4 (range 1-6) and the median for the mitoxantrone group was 5 (range 1-11). The planned treatment was delivered to 98% patients in the 3-weekly docetaxel group, 96% in the weekly docetaxel group and 99% in the mitoxantrone group. The proportion of patients in each of the groups receiving dose reductions was 12% in the 3-weekly docetaxel group, 9% in the weekly docetaxel group and 8% in the mitoxantrone group. There was a high level of crossover between groups in this trial, 27% of patients randomised to the 3-weekly docetaxel group received mitoxantrone, 24% of patients randomised to the weekly docetaxel group received mitoxantrone and 20% of patients randomised to the mitoxantrone group received docetaxel. The median length of follow-up was 20.8 months for the 3-weekly docetaxel group and 20.7 months for the other two groups.

More patients in the docetaxel groups stopped treatment because they had completed their treatment (46% in 3-weekly docetaxel group, 35% in weekly docetaxel group) than in the mitoxantrone group (25%), whilst the proportion of patients who stopped treatment due to progression of disease was higher in the mitoxantrone group (56%) compared to the docetaxel groups (38% in 3-weekly docetaxel group, 35% in weekly docetaxel group).

Quality of the trial comparing docetaxel plus prednisone with mitoxantrone plus prednisone

This was a randomised open-label comparative trial. The evaluation of the trial in relation to study quality is shown in Appendix 10.7. Full details of the quality checklist are available in Appendix 10.4.

Effectiveness of docetaxel plus prednisone versus mitoxantrone plus prednisone

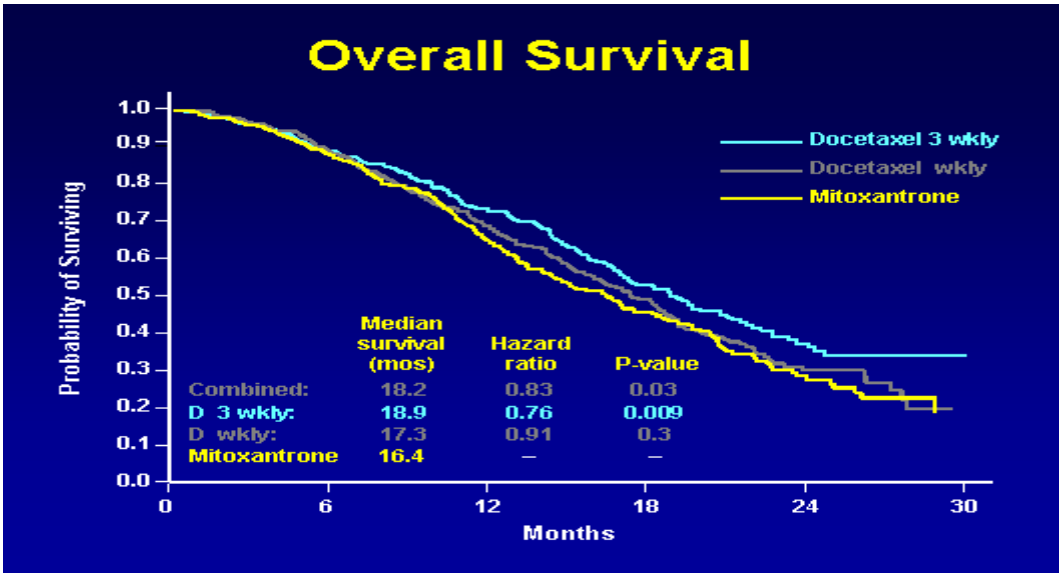
Overall survival

Overall survival was the primary end point for the trial and was defined as the time from the date of randomisation to the date of death from any cause or censored at the date of last contact. At the time of analysis 166/335 (50%) patients receiving 3-weekly docetaxel, 190/334 (57%) patients receiving weekly docetaxel and 201/337 (60%) patients receiving mitoxantrone had died.

There was a statistically significant benefit in terms of overall survival observed for the 3-weekly docetaxel group compared to the mitoxantrone group, HR for death=0.76 (95% CI: 0.62, 0.94, P=0.009). There was no statistically significant difference in overall survival between the weekly docetaxel group and the mitoxantrone group, HR for death=0.91 (95% CI: 0.75, 1.11).

The median overall survival was 18.9 months (95% CI: 17.0, 21.2) in the 3-weekly docetaxel group, 17.4 months (95% CI: 15.7, 19.0) in the weekly docetaxel group and 16.5 months (95% CI: 14.4, 18.6) in the mitoxantrone group. Figure 2 shows the Kaplan-Meier survival curves for the three groups.

Figure 2. Kaplan-Meier estimates of overall survival for docetaxel plus prednisone versus mitoxantrone plus prednisone[1]



[1] Source: *http://www.asco.org/ac/1,1003,_12-002511-00_18-0026-00_19-008928,00.asp*

Progression-free survival

No data were reported on progression-free survival in this trial.

Response rate

Tumour response was evaluated using the World Health Organisation criteria. These criteria are based on bidimensionally measurable lesions. Different response categories (complete response, partial response, stable disease and progression) are defined as an arbitrary percentage. However, tumour response was only reported for 412 patients. Of the 141 patients evaluated in the 3-weekly docetaxel group the response rate was 12% (95% CI: 7, 19), of the 134 patients evaluated in the weekly docetaxel group the response rate was 8% (95% CI: 4, 14) and of the 137 patients evaluated in the mitoxantrone group the response rate was 7% (95% CI: 3, 12). The difference in response rates between either of the docetaxel groups and the mitoxantrone group were not statistically significant; RR for response = 1.65 (95% CI: 0.78, 3.48) and 1.12 (95% CI: 0.49, 2.56) for each group compared to the mitoxantrone group respectively.

Health-related quality of life

Quality of life was assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire. Scores range from 0 to 156, with higher scores indicating a better quality of life. All patients who completed the questionnaire at baseline were included in the evaluation. A quality of life response was defined as a 16-point improvement in FACT-P score, compared to baseline, on two measures at least three weeks apart.

There was a statistically significant benefit in terms of quality of life observed for both the 3-weekly docetaxel group (22% response, 95% CI: 17, 27) and the weekly docetaxel group (23% response, 95% CI: 18, 28) compared with the mitoxantrone group (13% response, 95% CI: 9, 18). This was evaluated in 278, 270 and 267 patients respectively. Giving RR for quality of life of 1.67 (95% CI: 1.14, 2.45, p=0.009) and 1.75 (95% CI: 1.20, 2.56, p=0.005) for both comparisons respectively.

Pain

Pain was assessed using the PPI scale from the McGill-Melzack questionnaire. Scores range from 0 to 5, with higher scores indicating more pain. Analgesic use was assessed using a diary and an analgesic score was calculated by assigning a score of 1 for a standard dose of a non-narcotic analgesic and a score of 4 for a standard dose of a narcotic analgesic. Patients with a PPI score of at least 2, an analgesic score of at least 10, or both, at baseline were assessed for a pain response at three-week intervals. A pain response was defined as a two-point reduction in the PPI score from baseline without an increase in analgesic score, or a two-point reduction in the analgesic score, without an increase in pain score, maintained for at least three weeks.

There was a statistically significant benefit in terms of pain response observed for the 3-weekly docetaxel group (35% pain response, 95% CI: 27, 43) but not the weekly docetaxel group (31% pain response, 95% CI: 24, 39) compared with the mitoxantrone group (22% pain response, 95% CI: 16, 29). This was evaluated in 153, 154 and 157 patients respectively. Giving RR for pain response of 1.60 (95% CI: 1.12, 2.30, p=0.01) and 1.42 (95% CI: 0.97, 2.06, p=0.08) for both comparisons respectively. The median duration of pain response was 3.5 months (95% CI: 2.4, 8.1) in the 3-weekly docetaxel group, 5.6 months (95% CI: 2.8, 6.8) in the weekly docetaxel group and 4.8 months (95% CI: 4.4, indeterminate) in the mitoxantrone group.

PSA decline

PSA response was defined as a 50% or more reduction from baseline in serum PSA levels maintained for at least three weeks. There was a statistically significant benefit in terms of PSA response observed for both the 3-weekly docetaxel group (45% PSA response, 95% CI: 40, 51, P<0.0001) and the weekly docetaxel group (48% PSA response, 95% CI: 42, 54, P=0.0005) compared with the mitoxantrone group (32% PSA response, 95% CI: 26, 37). This was evaluated in 291, 282 and 300 patients respectively. Giving RR for PSA decline of 1.41 (95% CI: 1.14, 1.73, p<0.0001) and 1.5 (95% CI: 1.22, 1.84, p=0.0005) for both comparisons respectively. The median duration of PSA response was 7.7 months (95% CI: 7.1, 8.6) in the 3-weekly

docetaxel group, 8.2 months (95% CI: 6.3, 11.5) in the weekly docetaxel group and 7.8 months (95% CI: 5.4, 10.5) in the mitoxantrone group.

Adverse effects of treatment

Adverse events were measured using the Common Toxicity Criteria of the National Cancer Institute, version 2, and were reported for all 997 patients who received their planned treatment. Grade 3 or 4 adverse events were reported for 45.8% of the 3-weekly docetaxel group, 43% of the weekly docetaxel group and 34.6% of the mitoxantrone group. Eleven percent of patients in the 3-weekly docetaxel group, 16% of patients in the weekly docetaxel group and 10% of patients in the mitoxantrone group discontinued treatment due to adverse events. The proportion of patients who died as a result of treatment-related adverse events was 0.3% in the 3-weekly docetaxel group, 0.3% in the weekly docetaxel group and 1% in the mitoxantrone group.

The most common treatment related adverse events for the docetaxel treated participants were anaemia (67% in 3-weekly group), alopecia (65% in 3-weekly group, 50% in weekly group), fatigue (53% in 3-weekly group, 49% in weekly group), neutropenia (41% in 3-weekly group), nausea/vomiting (42% in 3-weekly group, 41% in weekly group), grade 3 or 4 neutropenia (32% in 3-weekly group, 2% in weekly group), diarrhoea (32% in 3-weekly group, 34% in weekly group), infection (32% in 3-weekly group), nail changes (30% in 3-weekly group, 37% in weekly group) and sensory neuropathy (30% in 3-weekly group, 24% in weekly group).

The most common treatment related adverse events for the mitoxantrone treated participants were anaemia (58%), neutropenia (48%), nausea/vomiting (38%) and fatigue (35%).

Table 3 shows the proportion of patients experiencing grade 3 or 4 adverse events.

Table 3. Grade 3 or 4 adverse events for docetaxel plus prednisone versus mitoxantrone plus prednisone

Adverse event	3-weekly docetaxel	Weekly docetaxel	Mitoxantrone
Anaemia	5%	5%	2%
Thrombocytopenia	1%	0%	1%
Neutropenia	32%*	2%**	22%
Fatigue	5%	5%	5%
Bone pain	8%	7%	10%
Infection	6%	6%	4%
Diarrhoea	2%	5%	1%

*P≤0.05 in comparison with mitoxantrone group
**P≤0.0015 in comparison with mitoxantrone group

Table 4. Summary results table for docetaxel plus prednisone versus mitoxantrone plus prednisone

	3-weekly docetaxel (A)	Weekly docetaxel (B)	Mitoxantrone (C)	Comparison
Mortality	166/335 (50%)	190/334 (57%)	201/337 (60%)	A vs C: HR=0.76 (95% CI: 0.62, 0.94) B vs C: HR=0.91 (95% CI: 0.75, 1.11)
Progression-free survival				Not reported
Response rate	17/141= 12% (7%, 19%)	11/134= 8% (4%, 14%)	10/137= 7% (3%, 12%)	A vs C: RR=1.65 (95% CI: 0.78, 3.48) B vs C: RR=1.12 (95% CI: 0.49, 2.56)
QoL response	61/278= 22% (17%, 27%)	62/270= 23% (18%, 28%)	35/267= 13% (9%, 18%)	A vs C: RR=1.67 (95% CI: 1.14, 2.45) B vs C: RR=1.75 (95% CI: 1.20, 2.56)
Pain response	54/153= 35% (27%, 43%)	48/154= 31% (24%, 39%)	35/157= 22% (16%, 29%)	A vs C: RR=1.58 (95% CI: 1.1, 2.27) B vs C: RR=1.40 (95% CI: 0.96, 2.03)
PSA decline	131/291= 45% (40%, 51%)	135/282= 48% (42%, 54%)	96/300= 32% (26%, 37%)	A vs C: RR=1.41 (95% CI: 1.14, 1.73) B vs C: RR=1.5 (95% CI: 1.22, 1.84)
AE: Discontinued: Grade ¾ : Died:	 11% 46% 0.3%	 16% 43% 0.3%	 10% 35% 1%	

4.3.2. Docetaxel plus prednisone plus estramustine versus mitoxantrone plus prednisone

One RCT was identified which aimed to evaluate PSA response and safety of two docetaxel-estramustine-prednisone schedules and one mitoxantrone-prednisone

schedule. In addition to the main publication of the trial,[28] the trial was also reported in three abstracts.[38-40] However, one of the abstracts contradicted the main trial report, so was not used in data extraction.[40]

Description of the trial comparing docetaxel plus prednisone plus estramustine with mitoxantrone plus prednisone

This multi-centre RCT included 130 men with mHRPC; 44 patients were randomised to receive a 1-hour i.v. infusion of docetaxel (70 mg/m^2 on day 2 every 21 days) plus oral estramustine (840 mg in 3 divided doses on days 1 to 5 and 8 to 12) plus prednisone, herein referred to as the one dose docetaxel group, 44 patients were randomised to receive a 30-minute i.v. infusion of docetaxel (35 mg/m^2 on days 2 and 9 every 21 days) plus oral estramustine (840 mg in 3 divided doses on days 1 to 5 and 8 to 12) plus prednisone, herein referred to as the two dose docetaxel group and 42 patients were randomised to receive mitoxantrone (12 mg/m^2 on day 1 every 21 days) plus prednisone, herein referred to as the mitoxantrone group. Patients in the docetaxel groups also received pre-medication with oral prednisolone (300 mg total dose) and 2 mg oral warfarin per day. Coumadin, an anticoagulant, was also given continuously to all patients. Patients were stratified by baseline PSA level and ECOG performance status score.

The baseline characteristics of patients across the three groups appear to have been reasonably well balanced in terms of tumour related symptoms, analgesic use, PSA level, sites of metastases, previous treatments and age. However, patients in the two dose docetaxel group had a trend for better ECOG performance status (59% had ECOG score of 0, compared with 40% in the one dose docetaxel group and 48% in the mitoxantrone group) and higher Gleason score (88% had Gleason score of 7-10, compared with 70% in the one dose docetaxel group and 67% in the mitoxantrone group). Patients in the mitoxantrone group had a trend for worse ECOG performance status (26% had ECOG score of 2, compared with 16% and 10% in the one dose and two dose docetaxel groups respectively) and time from diagnosis to random assignment was longer for patients in the mitoxantrone group (median 47 months, compared with 33 months in both of the docetaxel groups).

For inclusion in the trial patients had to have histologically proven metastatic adenocarcinoma of the prostate with documented disease progression, despite androgen deprivation; appearance of a new lesion and/or an increase of 25% or more of measurable metastases and/or the appearance of new foci on a radionuclide bone scan and/or three consecutive increases in PSA at least one week apart in the presence of castrate levels of testosterone. Patients were also required to have a life expectancy of at least three months and an ECOG performance status score of 0 to 2.

The median cumulative dose received by the one dose docetaxel group was 414 mg/m^2 (range 69-429), the median cumulative dose for the two dose docetaxel group was 403 mg/m^2 (range 66-423) and the median cumulative dose for the mitoxantrone group was 66 mg/m^2 (range 10-76). The estramustine cumulative doses were similar in the docetaxel groups. Three patients who were randomised did not receive the planned treatment and three patients required dose reductions (two in the one dose docetaxel group and one in the mitoxantrone group). There was a high level of crossover between groups in this trial, 16% of patients randomised to the one dose docetaxel group crossed over, 10% of patients randomised to the two dose docetaxel group crossed over and 48% of patients randomised to the mitoxantrone group crossed over. The difference in crossover between the treatment groups was statistically significant (P=0.00001). The median time on primary treatment was statistically significantly longer in the docetaxel groups compared with the mitoxantrone group (20.4 months, 95% CI: 17.5, 23.3 and 19.2 months, 95% CI: 15.7, 22.8, versus 11.6 months, 95% CI: 7.1, 16.2; P=0.003).

Quality of the trial comparing docetaxel plus prednisone plus estramustine with mitoxantrone plus prednisone

This was a small randomised open-label comparative trial. However, the method of randomisation was not reported, therefore cannot be assessed for adequacy and, whilst patients were stratified by baseline PSA level and ECOG performance status score, the performance status was not comparable at baseline between the three groups. The evaluation of the trial in relation to study quality is shown in Appendix 10.7.

Effectiveness of docetaxel plus prednisone plus estramustine versus mitoxantrone plus prednisone

Overall survival

Overall survival was defined as the time from study entry to death or the date of last follow-up. The authors state that survival analysis was performed at 12 months median follow-up (95% CI: 10.1, 13.8) when 99 deaths (78%) had occurred.

There was a non-statistically significant reduction in the relative risk of death for patients in the docetaxel groups compared with the mitoxantrone group, the reduction was 6% (95% CI: -2, 71) in the one dose docetaxel group compared with the mitoxantrone group and 14% (95% CI: -8, 32) in the two dose docetaxel group compared with the mitoxantrone group. We have assumed that the reduction in the relative risk of death is equivalent to the hazard ratio.

Three-year survival was 22% for the entire cohort. The length of survival was longer in the docetaxel groups; 18.6 months (95% CI: 14.9, 22.3) in the one dose docetaxel group and 18.4 months (95% CI: 14.1, 22.8) in the two dose docetaxel group, compared to the mitoxantrone group; 13.4 months (95% CI: 9.4, 17.5). However, this difference was not statistically significant.

The survival time of patients in the mitoxantrone group receiving salvage docetaxel therapy was 31.7 months (95% CI: 26.4, 36.9), compared with 7.5 months (95% CI: 4.9, 10.1) for patients receiving either no further chemotherapy or a non-docetaxel chemotherapy, however, this was only an exploratory analysis and the numbers of patients involved was not stated.

A multivariate analysis of the association of baseline factors with overall survival was statistically significant for baseline ECOG performance status (P=0.0001) and baseline haemoglobin level (cut-off at 11g/dL, P=0.006).

Progression-free survival

Time to progression was defined as the date of the first CT scan demonstrating a new lesion(s) or a 25% or more increase in the bi-dimensional measurements of previously

measurable disease, or, for patients with bone disease, a new lesion(s) on radionuclide bone scan. The median time to disease progression was 11.5 months (95% CI: 6.9, 16.9) for patients with measurable disease and 18.2 months (95% CI: 16.5, 21.8) for patients with bone disease only.

Response rate

Measurable disease response was defined in accordance with the World Health Organisation criteria. There were two complete responses and seven partial responses in the one dose docetaxel group, one complete response and two partial responses in the group two dose docetaxel group, and one complete response in the mitoxantrone group. The difference between groups was statistically significant (P=0.01).

Health-related quality of life

No data were reported on health-related quality of life in this trial.

Pain

'Clinical benefit' was defined as a reduction by at least one point in the pain index and/or performance status improvement by at least 1 point, measured using the pain control and analgesic consumption indices of the McGill pain questionnaire and ECOG performance status. Pain control was scored from 0 (no pain) to 4 (uncontrollable pain) and analgesic consumption was scored from 0 (no requirement) to 4 (regular narcotic analgesic use). Clinical benefit was not statistically significantly different between the docetaxel groups and the mitoxantrone group (33% for the one dose docetaxel group and 24% for the two dose docetaxel group versus 21% for the mitoxantrone group, p=0.06). Giving RRs for clinical benefit of 1.52 (95% CI: 0.74, 3.13) and 1.11 (95% CI: 0.50, 2.45) respectively.

ECOG performance status was statistically significantly improved in the docetaxel groups compared with the mitoxantrone group (60% and 48% versus 28%; P=0.01). The pain index was also improved in the docetaxel groups compared with the mitoxantrone group (40% and 29% versus 17%), but the difference was not statistically significant (P=0.06).

PSA decline

PSA decrease was the primary end point for the trial. There was a statistically significant benefit in terms of a 50% or more decrease in PSA level observed for both the one dose docetaxel group (29 patients; 67%) and the two dose docetaxel group (26 patients; 63%) compared with the mitoxantrone group (7 patients; 18%); P<0.002. Giving RRs for PSA decline of 3.95 (95% CI: 1.95, 8.00) and 3.71 (95% CI: 1.82, 7.58) respectively. The difference between groups was also statistically significant for a 75% or more decrease in PSA level (51% and 39% compared with 8%; P<0.002). The proportion of patients achieving normalisation of PSA level (less than 4ng/mL) was statistically significantly higher for the one dose docetaxel group compared with the mitoxantrone group (23% compared with 2%; P=0.01).

The median duration of PSA response was 8 months in the one dose docetaxel group, 8.3 months in the two dose docetaxel group and 6.4 months in the mitoxantrone group.

Time to PSA progression was defined as a 25% or more increase in PSA from baseline or a 50% or more increase in PSA from the lowest value achieved (increase must be at least 5ng/mL), confirmed by three successive measurements at 3-weekly intervals. The time to PSA progression was statistically significantly longer in the docetaxel groups; 8.8 months (95% CI: 6.9, 10.8) in the one dose docetaxel group, 9.3 months (95% CI: 7.5, 11.1) in the two dose docetaxel group, compared with 1.7 months (95% CI: 0.7, 2.7) in the mitoxantrone group (P=0.000001).

Adverse effects of treatment

Adverse events were measured using the Common Toxicity Criteria of the National Cancer Institute, version 1, and were reported for all 127 patients who received their planned treatment. Four patients discontinued treatment due to adverse events. One patient died as a result of corticosteroid pre-medication in the one dose docetaxel group.

Asthenia was the most common non-haematological adverse event, reported in 47% of patients in the one dose docetaxel group, 41% in the two dose docetaxel group and

26% of patients in the mitoxantrone group. Nail and skin toxicities occurred in approximately 14% of patients receiving docetaxel. Left ventricular ejection fraction (grade 1 to 2) occurred in 4 (10%) of patients receiving mitoxantrone.

Table 5 shows the proportion of patients experiencing grade 3 or 4 adverse events.

Table 5. Grade 3 or 4 adverse events for docetaxel plus prednisone plus estramustine versus mitoxantrone plus prednisone

Adverse event	One dose docetaxel	Two dose docetaxel	Mitoxantrone
Granulocytopenia	16 (37%)	0	20 (48%)
Granulocytopenic fever	0	0	3 (7%)
Anaemia	1 (2%)	0	3 (7%)
Thrombocytopenia	0	1 (2%)	1 (2%)
Nausea	1 (2%)	0	0
Vomiting	1 (2%)	0	0
Diarrhoea	3 (7%)	0	0
Thrombosis	3 (7%)	3 (7%)	0

Table 6. Summary results table for docetaxel plus prednisone plus estramustine versus mitoxantrone plus prednisone

	One dose docetaxel (A)	Two dose docetaxel (B)	Mitoxantrone (C)	Comparison
Mortality				A vs C: HR=0.94 (95% CI: 0.29, 1.02) B vs C: HR=0.86 (95% CI: 0.68, 1.08)
Progression-free survival				Not enough data
Response rate	9	3	1	Significant difference- not enough data
QoL response				Not reported
Pain response	14/43 (33%)	10/42 (24%)	9/42 (21%)	A vs C: RR=1.52 (95% CI: 0.74, 3.13) B vs C: RR=1.11 (95% CI: 0.50, 2.45)
PSA decline	29/43 (67%)	26/42 (63%)	7/42 (18%)	A vs C: RR=4.05 (95% CI: 1.99, 8.21) B vs C: RR=3.71 (95% CI: 1.82, 7.58)
AE: Discontinued: Grade ¾ : Died:	25* 1	4*	27*	4 in total

* May not be mutually exclusive

4.3.3. Docetaxel plus estramustine versus mitoxantrone plus prednisone

One RCT (SWOG 9916) was identified which aimed to determine whether docetaxel plus estramustine improves survival compared to mitoxantrone plus prednisone in men with mHRPC. In addition to the main publication of the trial,[29] there were two abstracts,[41, 43] and a protocol registered with ClinicalTrials.gov.[42]

Description of the trial comparing docetaxel plus estramustine with mitoxantrone plus prednisone

This multi-centre RCT included 770 men with mHRPC; 386 patients were randomised to receive an i.v. infusion of docetaxel (60 mg/m^2 on day 2 every 21 days, increased to 70 mg/m^2 if no grade 3 or 4 adverse events were observed during the first cycle) plus estramustine (three times daily on days 1-5), herein referred to as the docetaxel group and 384 patients were randomised to receive an i.v. infusion of mitoxantrone (12 mg/m^2 on day 1 every 21 days, increased to 14 mg/m^2 if no grade 3 or 4 adverse events were observed during the first cycle) plus prednisone (5 mg twice daily), herein referred to as the mitoxantrone group. Patients in the docetaxel group also received pre-medication with dexamethasone. Patients in the docetaxel group also received 2 mg warfarin and 325 mg aspirin per day after a protocol change 15 months into the 39 months of trial enrolment; numbers of patients enrolled before and after this date were not reported. Patients were stratified by type of progression (measurable versus PSA alone), grade of bone pain and SWOG performance status score. After enrolment 96 patients were found to be ineligible, therefore, 674 patients were included in the trial; 338 in the docetaxel group and 336 in the mitoxantrone group. The baseline characteristics of patients across the two groups appear to have been well balanced in terms of performance status, serum PSA level, grade of bone pain, type of progression, sites of secondary disease, race and age.

For inclusion in the trial patients had to have progressive metastatic disease, despite androgen-ablative therapy and cessation of anti-androgen treatment; progression of a bi-dimensionally measurable lesion as assessed within 28 days before study registration, progression of disease that could be evaluated but not measured as assessed within 42 days before registration, or an increase in serum PSA level over the baseline level in at least two consecutive samples obtained at least 7 days apart.

Patients were also required to have a SWOG performance-status score of 0-2 (3 was allowed if due to bone pain), and adequate renal, hepatic and cardiac function.

The median length of follow-up was 32 months. Six patients in the docetaxel group and four patients in the mitoxantrone group did not receive the assigned treatment. One patient in the mitoxantrone group also received intermittent radiotherapy, which was a major protocol deviation. Two patients in the docetaxel group and four patients in the mitoxantrone group discontinued treatment within one week.

Quality of the trial comparing docetaxel plus estramustine with mitoxantrone plus prednisone

This was a randomised open-label comparative trial. However, the methods of randomisation and concealment of allocation were not reported, therefore cannot be assessed for adequacy. The evaluation of the trial in relation to study quality is shown in Appendix 10.7.

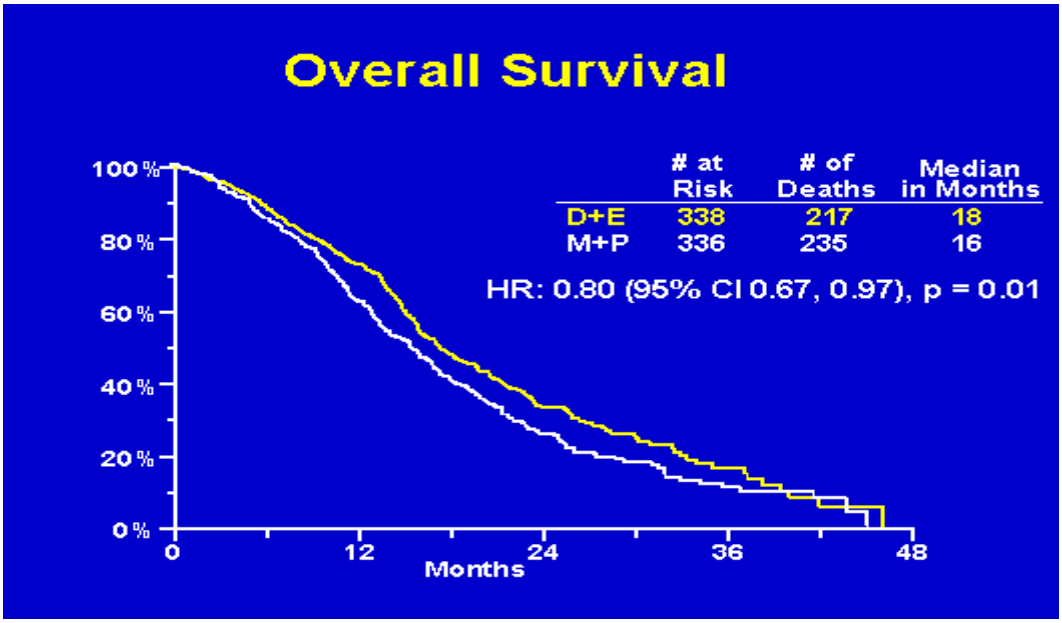
Effectiveness of docetaxel plus estramustine versus mitoxantrone plus prednisone

Overall survival

Overall survival was the primary end point for the trial and was defined as the time from the date of randomisation to the date of death from any cause or censored at the date of last contact. After a median follow-up of 32 months 217/338 (64%) patients receiving docetaxel and 235/336 (70%) patients receiving mitoxantrone had died.

There was a statistically significant benefit in terms of overall survival observed for the docetaxel group compared to the mitoxantrone group, HR for death=0.80 (95% CI: 0.67, 0.97). The median overall survival was 17.5 months in the docetaxel group and 15.6 months in the mitoxantrone group, this difference was statistically significant (P=0.02). Figure 3 shows the Kaplan-Meier survival curves for the two groups.

Figure 3. Kaplan-Meier estimates of overall survival for docetaxel plus estramustine versus mitoxantrone plus prednisone[2]



Progression-free survival

Time to progression was defined as the time from randomisation to the first occurrence of objective or PSA progression or death from any cause. At the time of analysis, 312 (92%) of patients in the docetaxel group and 311 (93%) of patients in the mitoxantrone group had progressed.

There was a statistically significant benefit in terms of time to disease progression observed for the docetaxel group compared to the mitoxantrone group, with HR for progression-free survival[3] = 1.302 (95% CI: 1.113, 1.523, p<0.001). The median time to disease progression was 6.3 months for the docetaxel group and 3.2 months for the mitoxantrone group.

[2] **Source:** *http://www.asco.org/ac/1,1003,_12-002511-00_18-0026-00_19-0010176,00.asp*

[3] Calculated from numbers of events and p-value presented in the trial publication.

Response rate

Objective responses were defined on the basis of the sum of bi-dimensional measurements of metastatic lesions. Confirmed objective response required a follow-up scan, a minimum of four weeks later that demonstrated a continued response.

A partial tumour response in measurable disease was reported for 196 patients. Of the 103 patients evaluated in the docetaxel group the response rate was 17%, of the 93 patients evaluated in the mitoxantrone group the response rate was 11%. The difference in response rates was not statistically significant with RR for response=1.54 (95% CI: 0.74, 3.18).

Health-related quality of life

No data were reported on health-related quality of life in this trial.

Pain

The authors report that there was no significant difference in pain relief between the two groups, as reported by the patients, however the data were not shown.

PSA decline

PSA response was defined as a 50% or more reduction from baseline in serum PSA levels. There was a statistically significant benefit in terms of PSA response observed for the docetaxel group (155/309 patients; 50%) compared with the mitoxantrone group (82/303 patients; 27%), giving RR for PSA decline of 1.85 (95% CI: 1.49, 2.30, $p<0.001$).

Adverse effects of treatment

Adverse events were measured using the Common Toxicity Criteria of the National Cancer Institute, version 2, and were reported for 658 patients. Grade 3 adverse events were reported for 114 patients in the docetaxel group and 63 patients in the mitoxantrone group. Grade 4 adverse events were reported for 62 patients in the docetaxel group and 46 patients in the mitoxantrone group. Statistically significantly more patients in the docetaxel group suffered grade 3 or 4 adverse events compared with the mitoxantrone group ($P<0.001$). Fifty-four (16%) patients in the docetaxel

group and 32 (10%) of patients in the mitoxantrone group discontinued treatment due to adverse events. Eight patients (2%) in the docetaxel group and four patients (1%) in the mitoxantrone group died as a result of treatment-related adverse events.

Table 7 shows the proportion of patients experiencing grade 3 or 4 adverse events.

Table 7. Grade 3 or 4 adverse events for docetaxel plus estramustine versus mitoxantrone plus prednisone

Adverse event	Docetaxel (n=330)		Mitoxantrone (n=328)	
	Grade 3	Grade 4	Grade 3	Grade 4
Cardiovascular*	37	10	16	6
Clotting	2	0	0	0
Dermatologic	1	0	1	0
Endocrine	0	0	1	0
Influenza-like symptoms	29	3	20	2
Nausea/vomiting*	61	5	16	1
Haematologic	17	47	18	33
Haemorrhage	11	2	6	0
Immunologic	3	0	0	0
Infection*	36	7	20	2
Liver	9	1	11	1
Lung	12	2	8	1
Metabolic*	14	6	2	0
Musculoskeletal	8	0	1	2
Neurologic*	21	2	5	0
Pain	34	1	18	5
Renal or bladder	8	0	3	0

*P<0.005 in comparison with mitoxantrone group

Table 8. Summary results table for docetaxel plus estramustine versus mitoxantrone plus prednisone

	Docetaxel group	Mitoxantrone group	Comparison
Mortality	217/338 (64%)	235/336 (70%)	HR=0.80 (95% CI: 0.67, 0.97)
Progression-free survival	312/338 (92%)	311/336 (93%)	HR=1.30 (95% CI: 1.11, 1.52)
Response rate	17/103 (17%)	10/93 (11%)	RR=1.54 (95% CI: 0.74, 3.18)
QoL response			Not reported
Pain response			No significant difference – data not shown.
PSA decline	155/309 (50%)	82/303 (27%)	RR=1.85

			(95% CI: 1.49, 2.30)
AE: Discontinued: Grade ¾ : Died:	 54/330 (16%) 176/330 (53%) 8/330 (2%)	 32/328 (10%) 109/328 (33%) 4/328 (1%)	

4.3.4. Mitoxantrone plus a corticosteroid versus a corticosteroid

Three RCTs (Berry et al., 2002,[30] CCI-NOV22,[31] and CALGB 9182[32]) were identified which investigated the effects of mitoxantrone plus a corticosteroid compared to the corticosteroid alone.

One RCT aimed to compare median time to treatment failure of men with asymptomatic mHRPC treated with mitoxantrone plus prednisone versus prednisone alone. In addition to the main publication[30] the trial was also reported as an abstract.[44]

One RCT (CCI-NOV22) aimed to investigate the benefit of mitoxantrone plus prednisone over prednisone alone with respect to the palliation of symptoms of mHRPC. In addition to the main publication of the trial[31] the trial was also reported as a retrospective analysis of the relationship between changes in serum PSA, palliative response and survival[45], two papers concentrating on the quality of life results [46, 48], three abstracts [47, 49, 50] and an approval package[20] from the Center for Drug Evaluation and Research at the United States Food and Drug Administration.

One RCT (CALGB 9182) aimed to evaluate survival duration of patients given mitoxantrone plus hydrocortisone over those given hydrocortisone alone. In addition to the main publication of the trial,[32] the trial was also reported as an abstract[51] and an approval package[20] from the Center for Drug Evaluation and Research at the United States Food and Drug Administration.

Description of the trials comparing mitoxantrone plus a corticosteroid with a corticosteroid

Berry et al:

This multi-centre RCT included 120 men with asymptomatic, progressive, mHRPC. Data were unavailable for one patient, 56 patients were randomised to receive an i.v. infusion of mitoxantrone (12 mg/m^2 every 21 days, for six cycles) plus 5 mg of oral

prednisone twice a day, herein referred to as the mitoxantrone group and 63 patients were randomised to receive 5 mg of oral prednisone twice a day, herein referred to as the prednisone group. The baseline characteristics of patients across the two groups appear to have been well balanced in terms of tumour characteristics, performance status, previous treatments, age, sites of secondary disease, race and stage of disease at diagnosis. However, there was a tendency for the patients in the mitoxantrone group to have a lower serum PSA level at baseline than those in the prednisone group.

For inclusion in the trial patients had to have asymptomatic hormone-refractory adenocarcinoma that had progressed on at least one hormonal regimen. Disease progression was defined as two-fold or greater increase in PSA over two measurements, 25% increase in number of bone scan lesions, or 25% increase in size of soft tissue lesions. Patients were also required to have adequate liver and cardiac function and an ECOG performance status between 0 and 2 to be eligible for inclusion in the trial. No crossovers were allowed in the trial, however administration of prednisone was continued after mitoxantrone therapy was discontinued.

CCI-NOV22:

This multi-centre RCT included 161 men with mHRPC; 80 patients were randomised to receive an i.v. infusion of mitoxantrone (12 mg/m^2 every 21 days) plus 5 mg of oral prednisone twice a day, herein referred to as the mitoxantrone group and 81 patients were randomised to receive 5 mg of oral prednisone twice a day, herein referred to as the prednisone group. Mitoxantrone therapy was continued until a cumulative dose of 140 mg/m^2 was attained. Dexamethasone and other steroid use were not permitted. Patients were stratified by performance status.

The baseline characteristics of patients across the two groups appear to have been well balanced in terms of age, sites of metastases, time since diagnosis, ECOG performance status, PPI pain score and overall quality of life. However, there was a tendency for the patients in the mitoxantrone group to have a higher serum PSA level, higher analgesic score and to have been treated with flutamide than the patients in the prednisone group.

For inclusion in the trial patients had to have metastatic adenocarcinoma of the prostate with symptoms including pain and disease progression despite standard hormonal therapy. Patients were also required to have an ECOG performance status score of 3 or better, with a life expectancy of at least three months and the ability to complete pain and quality of life questionnaires. Non-responding patients or those with progressive symptoms after treatment with prednisone alone for six weeks or more were allowed to crossover and receive mitoxantrone in addition to prednisone.

The median cumulative dose of mitoxantrone delivered was 73 mg/m^2 (range: 12 to 212 mg/m^2). The median number of cycles of mitoxantrone was 6.5 (range: 1 to 18), with a median dose of 12 mg/m^2 (range: 5.1 to 16.5 mg/m^2) of mitoxantrone per cycle. Mitoxantrone therapy was delayed for one or more cycles in seven (9%) patients originally randomised to receive mitoxantrone therapy. Of the 81 patients randomised to receive prednisone alone, 50 subsequently crossed-over to receive mitoxantrone in addition to the prednisone, five (10%) of these patients required a delay in mitoxantrone treatment. The median number of days before crossing over was 84 days (range: 11 to 324 days). There was one discontinuation in the prednisone only group due to toxicity.

CALGB 9182:

This RCT included 242 men with mHRPC; 119 patients were randomised to receive an i.v. infusion of mitoxantrone (14 mg/m^2 every 21 days) plus oral hydrocortisone (40 mg in two divided doses every day), herein referred to as the mitoxantrone group and 123 patients were randomised to receive oral hydrocortisone (40 mg in two divided doses every day) only, herein referred to as the hydrocortisone group. Patients were stratified by baseline disease status (measurable versus assessable) and ECOG performance status score. After the accrual of 60 patients, a third stratification by number of prior endocrine manipulations was added.

The baseline characteristics of patients across the groups appear to have been reasonably well balanced in terms of age, race, sites of metastases, years since diagnosis, PSA level and quality of life. However there was a tendency for the patients in the hydrocortisone group to have received more treatments with a

progesterone agent than the patients in the mitoxantrone group (18% of patients in the hydrocortisone group compared to 7% of patients in the mitoxantrone group).

For inclusion in the trial patients had to have metastatic adenocarcinoma of the prostate, with documented disease progression and had to have received no more than one prior endocrine manipulation. However the latter criterion was removed after the accrual of 60 patients for the trial, allowing patients with potentially poorer prognoses to be eligible for inclusion in the trial. Patients were also required to have adequate hepatic, renal and bone marrow functions.

Two patients in each treatment arm never started treatment and were excluded from the analyses. Four further participants; three in the hydrocortisone group and one in the mitoxantrone group were ruled ineligible for inclusion, but were included in the survival analysis only.

The median number of cycles of mitoxantrone administered was five. No crossovers were permitted, although alternative chemotherapy regimes were allowed after disease progression. Hydrocortisone treatment was continued in all patients, until disease progression or treatment failure, and was encouraged until death.

Quality of the trials comparing mitoxantrone plus a corticosteroid with a corticosteroid

Berry et al:

This was a small randomised open-label comparative trial. The methods used to assign patients to treatment groups and concealment of allocation were not reported, so the adequacy of these procedures cannot be assessed. Baseline comparability between the two groups appears to have been achieved. The evaluation of the trial in relation to study quality is shown in Appendix 10.7.

CCI-NOV22:

This was a reasonably small open-label comparative trial. The method used to assign participants to treatment groups was not reported, so the randomisation procedure cannot be assessed for adequacy. The two treatment groups were not completely

comparable at baseline. The evaluation of the trial in relation to study quality is shown in Appendix 10.7.

CALGB 9182:

This was a randomised open-label comparative trial. The methods of randomisation and concealment of allocation were not reported, therefore cannot be assessed for adequacy, and the number of prior treatments with a progesterone agent was not comparable at baseline between the two groups. The evaluation of the trial in relation to study quality is shown in Appendix 10.7.

Effectiveness of mitoxantrone plus a corticosteroid versus a corticosteroid

Berry:

Overall survival

Among the 119 patients analysed in this trial, 91 (76%) died within four years of the start of the study, 43 (77%) in the mitoxantrone group and 48 (76%) in the prednisone group. At 12 months, survival was 82% in the mitoxantrone group and 76% in the prednisone group. At 24 months, survival was 45% for the mitoxantrone group compared to 44% for patients in the prednisone group. Estimated overall survival from the start of treatment was 23 months (range: 3 to 49 months) in the mitoxantrone group compared to 19 months (range: 2 to 50 months) for the patients in the prednisone group. This difference in overall survival was not statistically significant, with an estimated HR for death[4] of 1.127 (95% CI: 0.747, 1.7, P=0.569).

Progression-free survival

Time to treatment failure (an aggregate endpoint defined by the time between start of treatment and occurrence of progression, removal from study or initiation of another treatment) was the primary outcome of the trial. At 12 and 24 months, progression-free survival was 36% and 13% for the mitoxantrone group compared to 15% and 10% for the prednisone group respectively.

[4] Calculated from numbers of events and p-value presented in the trial publication.

The median time to progression was 8.1 months (range:1 to 50 months) for patients in the mitoxantrone group compared to 4.1 months (range:1 to 37 months) for those in the prednisone group. There was a statistically significant benefit for the mitoxantrone group compared to the prednisone group in terms of progression-free survival (p=0.018), with an estimated HR for progression[5] of 0.64 (95% CI: 0.48, 0.86).

Response rate

For the 17 patients with measurable tumours (8 patients in the mitoxantrone group, 9 in the prednisone group) objective response was reported. There were no complete responses recorded in either group, two patients (25%) in the mitoxantrone group and two patients (22%) in the prednisone group experienced partial responses.

Health-related quality of life

No data on health-related quality of life were reported for this trial.

Pain

No data on pain were reported for this trial.

PSA decline

PSA response was defined as a 50% or more reduction from baseline in serum PSA levels for at least two months, with stable or improved performance status for at least two weeks. There was a statistically significant benefit in terms of PSA response observed for the mitoxantrone group compared with the prednisone group; 27 patients (48%) and 15 patients (24%) achieved a PSA response respectively, giving a RR for PSA decline of 2.025 (95% CI: 1.206, 3.401, p=0.007). The median time to PSA response was 2.2 months (range: 0.6 to 4.6) in the mitoxantrone group and 2.2 months in the prednisone group (range: 0.2 to 7.1).

[5] Estimated from the Kaplan-Meier curve for progression-free survival presented in the trial publication.

Adverse effects of treatment

Adverse events were measured using the Common Toxicity Criteria of the National Cancer Institute, and any adverse events greater than grade 3 reported. There were no treatment related deaths reported in either group.

Table 9 shows the proportion of patients experiencing grade 3 or 4 adverse events.

Table 9. Grade 3 or 4 adverse events for mitoxantrone plus prednisone versus prednisone

Adverse event	Mitoxantrone group	Prednisone group	RR (95% Confidence interval)
Neutropenia	27 (48%)	6 (10%)	5.0625 (2.256, 11.358)
Leucopenia	11 (20%)	5 (8%)	2.475 (0.916, 6.687)
Pulmonary complications	4 (7%)	4 (6%)	1.125 (0.295, 4.289)
Asthenia	3 (5%)	3 (5%)	1.125 (0.237, 5.35)
Renal complications	1 (2%)	3 (5%)	0.375 (0.04, 3.503)
Gastrointestinal complications	3 (5%)	1 (2%)	3.375 (0.361,31.526)
Sepsis	2 (4%)	0	
Melanoma	1 (2%)	0	

Some patients had more than 1 toxic reaction.

Table 10. Summary results table for mitoxantrone plus prednisone versus prednisone

	Mitoxantrone group	Prednisone group	Comparison*
Mortality	43/56 (77%)	48/63 (76%)	HR=1.13 (95% CI: 0.75, 1.7)
Progression-free survival			HR=0.64 (95% CI: 0.48, 0.86)
Response rate	2/8 (25%)	2/9 (22%)	RR=1.13 (95% CI: 0.20, 6.24)
QoL response			Not reported
Pain response			Not reported
PSA decline	27/56 (48%)	15/63 (24%)	RR=2.03 (95% CI: 1.21, 3.40)
AE: Discontinued: Grade ¾ : Died:	 Not reported Not evaluable 0	 Not reported Not evaluable 0	

*All comparisons are M+P vs. P, so HR<1 favours M+P if the outcome is undesirable (e.g. mortality)

CCI-NOV22:

Overall survival

Overall survival was defined as the time from the date of first treatment until the date of death. At the time of analysis, there were 140 deaths in total, with no statistically significant difference between the two treatment groups (p=0.27). This difference was reported to be in favour of the mitoxantrone group, however the number of deaths in each group were not reported. The median survival time for all patients in the trial was 10 months, again with no statistically significant difference between treatment groups (p=0.15). The estimated HR for death[6] = 0.907 (95% CI: 0.691, 1.192).

Progression-free survival

Disease progression was defined as; an increase in the pain score of at least one point recorded at two consecutive measurements, an increase in analgesic score of at least 25% at two consecutive visits, unequivocal evidence of new lesions or progression of existing lesions, or a requirement for radiotherapy. Pain was assessed using the Present Pain Intensity (PPI) scale from the McGill-Melzack questionnaire. Scores range from 0 to 5, with higher scores indicating more pain. Analgesic use was assessed using a diary and an analgesic score was calculated by assigning a score of 1 for a standard dose of a non-narcotic analgesic and 2 for a standard oral dose of a narcotic. The analgesic scores were averaged for the last 7 days of each 21 day cycle.

Data on time to progression were available for 147 participants from the approval package[20]. At the time of analysis, treatment had failed for 43 participants in the mitoxantrone group and for 60 of the patients in the prednisone group. There was a statistically significant benefit in terms of time to progression for those in the mitoxantrone group over those in the prednisone group, estimated HR for time to progression[7]=2.153 (95% CI: 1.463, 3.168, p=0.0001).

The median time to progression was 148 days for those in the mitoxantrone group and 62 days for those in the prednisone group.

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[6] Estimated from the Kaplan-Meier survival curve presented in the trial publication.

[7] Calculated from numbers of events and p-value presented in the trial publication.

Response rate

The primary outcome for this trial was palliative response, defined as a 2-point improvement in pain score without an increase in analgesic score maintained for two consecutive visits, at least three weeks apart. Those participants with a baseline pain score of one or lower, were required to have a complete reduction in pain score. A secondary criterion for palliative response was defined as a 50% or more decrease in analgesic score without an increase in pain score.

There were 23 patients in the mitoxantrone group and 10 in the prednisone group that responded to the primary criterion for response, giving response rates of 29% (95% CI: 19%, 40%) and 12% (95% CI: 6%, 22%) respectively. There was a statistically significant benefit for the mitoxantrone group compared to the prednisone group, estimated RR for response=2.329 (95% CI: 1.186,4.574, p=0.01).

There was also a statistically significant benefit in terms of median duration of palliative response for those in the mitoxantrone group; 43 weeks, compared to those in the prednisone group; 18 weeks (p<0.0001).

An additional seven patients in each treatment arm satisfied the secondary criterion stipulated for palliative response. The mean duration in these patients was 33 weeks for those in the mitoxantrone group compared to 24 weeks for those in the prednisone group.

Out of the 50 patients who crossed over to receive mitoxantrone therapy after originally being randomised to prednisone alone, 11 (22%) of patients experienced a palliative response. The median duration for this response was 18 weeks (range: 9 to 69).

Health-related quality of life

Quality of life was assessed using three separate instruments. The Prostate Cancer-Specific Quality-of-life Instrument (PROSQOLI), which consists of nine linear analogue self-assessment (LASA) scales relating to various areas of quality of life with scores ranging from 0 to 10, with higher scores indicating a better quality of life

was used. As was the core questionnaire with 30 ordinal scale items including assessment of various domains associated with quality of life, from the European Organisation for Research and Treatment of cancer (EORTC/QLQ-C30), with scores ranging from 0 to 100, with 100 indicating excellent quality of life. This latter instrument was supplemented by a trial specific questionnaire, the QOLM-P14, with scores ranging from 0 to 100, with higher scores indicating more severe symptoms.

A total of 71 patients receiving mitoxantrone were included in the analyses of health-related quality of life as reported by Osoba et al.[46] These analyses showed that compared with baseline, this group experienced significant improvements in physical functioning, social functioning, global quality of life, pain, anorexia, constipation, impact of pain on mobility, degree of pain relief, drowsiness ($0.0001 < P < 0.009$). The duration of improvements ranged from 11 to 19 weeks.

A total of 62 patients receiving prednisone were included in the analyses of health-related quality of life as reported by Osoba et al.[46] These analyses showed that compared with baseline, this group experienced significant improvements in social functioning, global quality of life, nausea & vomiting, anorexia ($0.003 < P < 0.007$) and impact of pain on mobility ($P = 0.01$). The duration of improvements ranged from 3 to 7 weeks.

A total of 35 patients receiving prednisone then crossing over to receive mitoxantrone were included in the analyses of health-related quality of life as reported by Osoba et al.[46] These analyses showed that compared with baseline, this group experienced significant improvements in pain, insomnia & impact of pain on mobility ($0.0001 < P < 0.01$). The duration of improvement ranged from 4 to 26 weeks.

There was a statistically significant benefit for the mitoxantrone group compared to the prednisone group in terms of the duration of improvements of more than ten points from baseline in social functioning, pain, impact of pain on mobility, pain relief, insomnia & drowsiness ($0.004 < P < 0.048$).

Pain

Due to the definitions of progression-free survival and response rate, data on pain have been reported under these headings (see above).

PSA decline

There were 57 patients in the mitoxantrone group and 54 patients in the prednisone group for whom at least two PSA measurements were recorded (one at baseline and at least one subsequent visit). There were no statistically significant differences with respect to PSA decline between the two groups; RR for PSA decline=1.5 (0.807, 2.787, p=0.11). Of the 57 patients in the mitoxantrone group included in the analysis, 28 (49%) achieved a PSA decline of 25% or more, of these 19 (33%) achieved a decline of at least 50% and 13 (23%) of these achieved a decline of 75% or more. Of the 54 patients in the prednisone group included in the analysis, 25 (46%) achieved a PSA decline of 25% or more, of these 12 (22%) achieved a decline of at least 50% and 5 (9%) of these achieved a decline of 75% or more.

Adverse effects of treatment

Limited information on adverse effects of treatment was reported in the original trial publication. Only one patient randomised to the prednisone group was reported to have discontinued treatment due to toxicity. There were five patients in the mitoxantrone group that received cumulative doses of 116 to 214 mg/m^2 of mitoxantrone that developed cardiac abnormalities, however there were no deaths resulting from this. All 130 patients who received mitoxantrone therapy (including those who crossed over) were assessed using the WHO criteria for toxic side effects. As data were reported in the FDA report[20] for the prednisone group prior to crossover, comparisons with the adverse effects of mitoxantrone can be made.

Data on adverse effects of treatment presented in the approval package[20] report that there were 43 serious adverse events, either related or unrelated to study drugs experienced by 37 patients; 22 in the mitoxantrone group and 15 in the prednisone group (7 of these patients had crossed over). A total of 11 patients in the mitoxantrone group withdrew from the trial due to toxicity and one patient

randomised to receive prednisone alone withdrew due to toxicity after crossing over to receive mitoxantrone.

Table 11 shows the proportion of patients experiencing grade 3 or 4 adverse events (presented in the FDA report).

Table 11. Grade 3 or 4 adverse events for mitoxantrone plus prednisone versus prednisone

	Mitoxantrone group (N=80)	Prednisone group (N=81) (prior to crossover)
Leucopenia	15%	0
Neutropenia	54%	1%
Thrombocytopenia	1%	0
Anaemia	1%	-

Table 12. Summary results table for mitoxantrone plus prednisone versus prednisone

	Mitoxantrone group	Prednisone group	Comparison
Mortality			HR=0.91 (95% CI: 0.69, 1.19)
Progression-free survival	43/77 (56%)	60/70 (86%)	HR=2.15 (95% CI: 1.46, 3.17)
Response rate	23/80 (29%)	10/81 (12%)	RR=2.33 (95% CI: 1.19,4.57)
QoL response			Variety of measures
Pain response			See response rate
PSA decline	19/57 (33%)	12/54 (22%)	RR=1.5 (95% CI: 0.81, 2.79)
AE: Discontinued: Grade ¾ : Died:	 11 22 Not reported	 1 15 Not reported	

CALGB 9182:

Overall survival

Overall survival was the primary end point for the trial, defined as the time between randomisation and death, for living patients the survival time was censored at the time of last follow-up. At the time of analysis, there had been 58 deaths out of 119 patients in the mitoxantrone group and 68 deaths out of 123 patients in the hydrocortisone group.

There was no statistically significant benefit in terms of overall survival observed for the mitoxantrone group compared to the hydrocortisone group, unadjusted HR for death[8]=1.05 (95% CI: 0.74, 1.49, P=0.77). When adjusting for baseline PSA, haemoglobin, lactate dehydrogenase and alkaline phosphatase levels, there was still no statistically significant difference in overall survival between groups, HR for death=1.0 (95% CI: 0.8, 1.3, p=0.976).

The median overall survival was 12.3 months in the mitoxantrone group and 12.6 months for the hydrocortisone group.

Progression-free survival

Time to disease progression was defined as the time from randomisation to a worsening of performance status by at least one point, or the appearance of two or more new lesions on bone scan, or an increase of at least 100% in serum PSA level from baseline. At the time of analysis, 56 patients in the mitoxantrone group and 71 patients in the hydrocortisone group had progressed.

There was a statistically significant benefit in terms of time to disease progression for the mitoxantrone group compared to the hydrocortisone group, HR for time to progression[9]=1.502 (95% CI: 1.061,2.127, p=0.0218)

The median time to disease progression was 3.7 months for the mitoxantrone group compared with 2.3 months for the hydrocortisone group.

Response rate

A complete response was defined as the disappearance of all disease by scans, and normalisation of PSA levels, sustained for at least 28 days. For those with measurable tumours, partial response was defined as a 50% or more reduction in bidimensional measurements for at least four weeks, or an 80% or more reduction of serum PSA

[8] Calculated from numbers of events and p-value presented in the trial publication.

[9] Calculated from number of events and p-value presented in the trial publication.

level from baseline sustained for at least six weeks. For patients with assessable and bone-only disease, the latter criteria only defined a partial response.

The analysis of response rates was based only on the 234 participants receiving study treatment, of these 69 patients had measurable tumours. No complete responses were observed in either group. Partial responses were observed in eight (7%) patients in the mitoxantrone group and five (4%) patients in the hydrocortisone group. There was no statistically significant difference in terms of response rate between groups; RR for response = 1.654 (95% CI: 0.557, 4.912, p=0.375).

Health-related quality of life

Health-related quality of life was assessed using five instruments. The Functional Living Index-Cancer (FLIC) with scores ranging from 0 to 7 was used to provide a global assessment of quality of life. Four other health-related quality of life instruments were used to provide in-depth evaluations of cancer-related symptoms, sexual and urological issues, problems with everyday activities and the impact of pain on activities such as sleep and normal work.

A total of 155 (66%) patients were assessed at baseline and at least one follow-up. The estimated treatment effects showed that there was no statistically significant benefit for the mitoxantrone group compared to the hydrocortisone group in terms of global quality of life as assessed by the FLIC questionnaire (p=0.12). Some of the items of the questionnaires did show statistically significant benefits for the mitoxantrone group compared to the hydrocortisone group in relation to emotional state and family disruption (p=0.04 and 0.02 respectively as assessed by FLIC), and severity of pain (p=0.03 as assessed by the symptom distress scale).

Pain

Data on pain were measured and reported with the health-related quality of life assessments. Specific items assessed by the quality of life instruments and reported were the total impact of pain, frequency of pain, severity of pain and pain from cancer, only the latter item showed a tendency for those in the hydrocortisone group to have a better quality of life than those in the mitoxantrone group.

PSA decline

PSA decline was defined as at least a 50% reduction and at least an 80% reduction of serum PSA from baseline at a follow-up examination between four and eight weeks. A post-hoc analysis was also performed to determine the maximum PSA decrease over the duration of the whole trial. The original analysis of PSA decline included 187 patients for whom PSA measurements were available, and the post-hoc analysis included 228 participants.

Between 4 and 8 weeks, 18 (18.7%) patients in the mitoxantrone group had achieved a PSA decline of at least 50%, and of these 4 (4.2%) patients achieved a PSA decline of 80% or more. During the same time interval, 13 (14.3%) patients in the hydrocortisone group achieved a PSA decline of at least 50%, and of these 4 (4.3%) patients achieved a PSA decline of 80% or more. These differences were not statistically significant (p=0.412).

The post-hoc analysis of PSA decline over the duration of the whole trial showed that 42 (37.5%) patients in the mitoxantrone group achieved a 50% or greater decline in PSA, and of these 22 (19.6%) patients experienced a decline of 80% or more. In the hydrocortisone group 25 (21.5%) patients had PSA decreases of 50% or more, and of these, 11 (9.5%) patients had declines of 80% or more. There was a statistically significant benefit for the mitoxantrone group compared to the hydrocortisone group with respect to PSA decline throughout the trial, both for declines of at least 50% (p=0.008) and declines of at least 80% (p=0.029).

Adverse effects of treatment

Grade 3 and 4 specific toxicities were reported for 206 (86%) patients. There were no observed treatment related deaths in either group. The most common treatment related adverse event reported for the mitoxantrone group was haematopoietic toxicity, occurring in approximately 70% of patients. There were statistically significant differences between the two treatment groups in terms of the haematopoietic toxicities reported (p<0.01).

Table 13 shows the proportion of patients experiencing grade 3 or 4 haematopoietic toxicities.

Table 13. Grade 3 or 4 haematopoietic adverse events for mitoxantrone plus hydrocortisone versus hydrocortisone

	Mitoxantrone group	Hydrocortisone group
White Blood Count	59%	1%
Platelets	6%	0
Granulocytes/bands	63%	1%
Lymphocytes	70%	15%

Table 14. Summary results table for mitoxantrone plus hydrocortisone versus hydrocortisone

	Mitoxantrone group	Hydrocortisone group	Comparison
Mortality	58/119 (49%)	68/123 (55%)	HR=1.05 (95% CI: 0.74, 1.49)
Progression-free survival	56/119 (47%)	71/123 (58%)	HR=1.502 (95% CI: 1.06,2.13)
Response rate	8/119 (7%)	5/123 (4%)	RR=1.654 (95% CI: 0.56,4.91)
QoL response			Variety of measures
Pain response			See QoL response
PSA decline (≥50% over trial)	42/112 (38%)	25/116 (22%)	RR=1.74 (95% CI: 1.14, 2.66)
AE: Discontinued: Grade ¾ : Died:	 Not reported Not evaluable 0	 Not reported Not evaluable 0	 Reported for 206 (86%)

4.3.5. Mitoxantrone plus prednisone plus clodronate versus mitoxantrone plus prednisone plus placebo

One RCT was identified which aimed to compare the incidence of palliative response in patients with mHRPC treated with mitoxantrone plus prednisone plus clodronate with that of patients treated with mitoxantrone plus prednisone plus placebo. In addition to the main publication of the trial,[33] there was an abstract,[53] and a protocol registered with the National Cancer Institute clinical trials register.[52]

Description of the trial comparing mitoxantrone plus prednisone plus clodronate with mitoxantrone plus prednisone plus placebo

This multi-centre double blind RCT included 227 men with mHRPC; 115 patients were randomised to receive an i.v. infusion of mitoxantrone (12 mg/m^2 every 21 days) plus prednisone (5 mg twice daily) plus an i.v. infusion of clodronate (1,500 mg over three hours every 21 days), herein referred to as the clodronate group and 112 patients were randomised to receive an i.v. infusion of mitoxantrone (12 mg/m^2 every 21 days) plus prednisone (5 mg twice daily) plus an i.v. infusion of placebo (1,500 mg normal saline over three hours every 21 days), herein referred to as the placebo group. Patients were stratified by pain level and previous corticosteroid use. After enrolment 18 patients were found to be ineligible, therefore, 209 patients were included in the trial; 104 in the clodronate group and 105 in the placebo group. The baseline characteristics of patients across the two groups appear to have been reasonably well balanced in terms of serum PSA level, pain score, previous corticosteroid use and age. However, patients in the placebo group had a trend for better ECOG performance status (13% had ECOG score of 0, compared with 9% in the clodronate group, 20% had ECOG score of 2, compared with 29% in the clodronate group) and lower daily morphine equivalents (median 57 mg, compared with 70 mg in the clodronate group).

For inclusion in the trial patients had to have radiologically confirmed progressive bone disease and castrate levels of testosterone; presence of new lesions on bone scan, increased isotope uptake at previous sites of disease or increasing bone pain. Patients were also required to have an ECOG performance status score of less than 3, baseline left ventricular ejection fraction more than 50% and the ability to complete the pain and quality of life forms. Patients were also required to have a score of at least 1 on the PPI scale of the McGill-Melzack Pain Questionnaire and stable analgesic use; no more than 25% variance in analgesic score in the week before randomisation.

Fifty percent of patients in the clodronate group and 44% of patients in the placebo group received at least seven cycles of therapy. One patient in the clodronate group received placebo. The reasons for discontinuation of treatment were patient request for 11 patients in the clodronate group and 10 patients in the placebo group,

progressive disease for 58 patients in the clodronate group and 68 patients in the placebo group and protocol violation for 14 patients in the clodronate group and 10 patients in the placebo group.

Quality of the trial comparing mitoxantrone plus prednisone plus clodronate with mitoxantrone plus prednisone plus placebo

This was a randomised double blind comparative trial. However, the method of concealment of allocation was not reported, therefore cannot be assessed for adequacy. The evaluation of the trial in relation to study quality is shown in Appendix 10.7.

Effectiveness of mitoxantrone plus prednisone plus clodronate versus mitoxantrone plus prednisone plus placebo

Overall survival

Overall survival was defined as the time from the date of randomisation to the date of death or censored at the date when patient was last known to be alive. Eighty-seven of the 104 patients in the clodronate group and 89 of the 105 patients in the placebo group died. The hazard ratio for death (placebo to clodronate) was 0.95 (95% CI: 0.71, 1.28). The median overall survival was 10.8 months (95% CI: 8.2, 13.0) in the clodronate group and 11.5 months (95% CI: 8.8, 14.4) in the placebo group.

Overall survival was statistically significantly associated with a baseline haemoglobin level of more than 100g/L compared with those with a baseline haemoglobin level of less than 100g/L, hazard ratio for death was 0.52 (95% CI: 0.35, 0.78; P=0.001).

Progression-free survival

Symptomatic progression free survival was defined as the time from randomisation to the date of progression (pain or other symptoms), or date of death for those who died without progression. Ninety-five patients in the clodronate group and 101 patients in the placebo group developed progression. The hazard ratio of developing progression (placebo to clodronate) was 1.237 (95% CI: 0.934, 1.64). The median symptomatic progression free survival was 5.0 months (95% CI: 4.1, 6.8) in the clodronate group and 4.0 months (95% CI: 2.9, 4.9) in the placebo group.

Symptomatic progression free survival was statistically significantly associated with a baseline haemoglobin level of more than 100g/L compared with those with a baseline haemoglobin level of less than 100g/L, HR=0.67 (95% CI: 0.46, 0.99; P=0.04).

Response rate

Palliative response was the primary end point for the trial, defined as either a 2-point reduction in PPI without an increase in analgesic score or evidence of disease progression, or more than 50% decrease in analgesic score without an increase in PPI, on two consecutive evaluations at least three weeks apart. There was no statistically significant difference in palliative response rate between the clodronate group and the placebo group (43% versus 37.5%, P=0.52). This gives a RR for response of 1.14 (95% CI: 0.81, 1.59). However, when looking at the subgroup of patients with a baseline PPI score of 3 or 4 (moderate pain), as opposed to 1 or 2 (mild pain), the difference in palliative response rate between the clodronate group and the placebo group was statistically significant (58% versus 26%, OR for palliative response for the clodronate arm compared with the placebo arm=4.6, P=0.04). The median duration of palliative response was 6.2 months (95% CI: 5.0, 9.2) for the clodronate group and 6.4 months (95% CI: 4.0, 9.6) for the placebo group, the difference was not statistically significant.

Health-related quality of life

Health-related quality of life response was defined as a 1 cm improvement on a 10 cm visual analogue scale, maintained on two consecutive visits, no less than three weeks apart. There was no statistically significant difference in health-related quality of life response between the clodronate group (37.5%) and the placebo group (42%). This gives a RR for quality of life of 0.89 (95% CI: 0.64, 1.25).

Pain

Pain was assessed using the PPI scale from the McGill-Melzack questionnaire. Scores range from 0 to 5, with higher scores indicating more pain. Analgesic use was assessed using a diary and an analgesic score was calculated by assigning a score of 1 for a standard dose of non-opioids and a score of 2 for opioid doses of morphine 10

mg equivalents. Pain response was defined as a 2-point or more reduction in PPI score in comparison with baseline, irrespective of analgesic response. Analgesic response was defined as a 50% or more decrease in analgesic score from baseline with no increase in pain. There was no statistically significant difference in pain response or analgesic response between the clodronate group (33% pain response, 33% analgesic response) and the placebo group (26% pain response, 30% analgesic response). Giving an RR for pain response=1.27 (95% CI: 0.83, 1.95). Thirty-one percent of patients in the clodronate group no longer required analgesics for two consecutive cycles, compared with 25% in the placebo group; again the difference was not statistically significant.

PSA decline

PSA response was defined as a 50% or more reduction from baseline in serum PSA levels for at least two visits. 30 patients in the clodronate group had a PSA response (29.7%) compared with 30 patients (28.6%) in the placebo group. Giving an RR for PSA decline of 1.04 (95% CI: 0.68, 1.59)

Adverse effects of treatment

Adverse events were measured using the Expanded Common Toxicity Criteria of the National Cancer Institute. There were no treatment related deaths. Three patients in the clodronate group and two patients in the placebo group discontinued treatment due to adverse events. Table 15 shows the numbers of patients experiencing grade 3 or 4 adverse events.

Table 15. Grade 3 or 4 adverse events for mitoxantrone plus prednisone plus clodronate versus mitoxantrone plus prednisone plus placebo

Adverse event	Clodronate	Placebo
Granulocytopenia	14	14
Anaemia	8	5
Thrombocytopenia	2	4
Cardiovascular	0	3
Nausea/vomiting	9	7
Headache	4	1
Shortness of breath	4	7
Infection	7	3

Table 16. Summary results table for mitoxantrone plus prednisone plus clodronate versus mitoxantrone plus prednisone plus placebo

	Clodronate group	Placebo group	Comparison
Mortality	87/104 (84%)	89/105 (85%)	HR=0.95* (95% CI: 0.71, 1.28)
Progression-free survival	95/104 (91%)	101/105 (96%)	HR=1.24 (95% CI: 0.93, 1.64)
Response rate	43/101 (43%)	39/104 (38%)	RR=1.14 (95% CI: 0.81, 1.59)
QoL response	39/104 (38%)	44/105 (42%)	RR=0.89 (95% CI: 0.64, 1.25)
Pain response	34/104 (33%)	27/105 (26%)	RR=1.27 (95% CI: 0.83, 1.95)
PSA decline (≥50% over trial)	30/101 (30%)	30/105 (29%)	RR=1.04 (95% CI: 0.68, 1.59)
AE: Discontinued: Grade ¾ : Died:	 3 0	 2 0	

*HR<1 favours placebo group.

4.4. Evidence synthesis

In this section we first describe the combined results of the three studies evaluating the relative effectiveness of mitoxantrone plus a corticosteroid in comparison to a corticosteroid alone. Next we present the results of each intervention described in the included trials using mitoxantrone plus a corticosteroid as the common comparator. Finally we present the results of any indirect pairwise comparisons that may be of interest.

4.4.1. Pooled estimate of effectiveness of mitoxantrone plus a corticosteroid versus a corticosteroid

In order to assess the overall effectiveness of mitoxantrone plus a corticosteroid compared to a corticosteroid alone it is possible to estimate a pooled treatment effect in a meta-analysis. However there are a number of differences between the three studies that may limit the interpretation of the estimate of the pooled treatment effect.

Outcomes were measured differently in the three trials

The primary outcomes in the three studies were all different; Berry et al. designed the trial to investigate the median time to treatment failure, CCI-NOV22 was designed to examine the effects on the palliation of symptoms and CALGB 9182 was designed to determine the survival duration. Although these differences in objectives are unlikely

to affect the results of any meta-analyses, it may mean that the trials will have been designed differently, which could affect the appropriateness of using pooling techniques.

The definitions and the measurements of outcomes varied across the three trials. Overall survival was the only outcome that was measured in a sufficiently similar manner to allow a pooled estimate. It is only appropriate to estimate a pooled treatment effect if the outcomes were measured and defined in a sufficiently similar manner across all trials.

Crossovers were permitted in CCI-NOV22

The CCI-NOV22 trial allowed patients originally randomised to receive prednisone alone to cross over to receive additional mitoxantrone after they had progressed or remained stable for at least 6 weeks on prednisone therapy. However, crossovers were not permitted in either the CALGB 9182 trial or in the trial by Berry et al.

Including crossovers in intention to treat analyses can result in 'dilution' of the true effects of a treatment, as patients are analysed as randomised. For example if mitoxantrone plus prednisone is more effective than prednisone alone, then any analyses would be less conclusive. This is because in that situation, it is likely that there would be a number of patients randomised to receive prednisone alone crossing over and receiving mitoxantrone as well later in the trial. If any of these patients that crossed over then responded to the mitoxantrone therapy, they would still be analysed as randomised i.e. to prednisone alone. This therefore would attribute an effect to prednisone rather than mitoxantrone, thus diluting the true estimate of treatment effect of mitoxantrone. However, in this case the study that allowed crossovers had a stronger treatment effect in favour of mitoxantrone plus prednisone than the two studies that did not allow crossovers.

Hydrocortisone was used in CALGB 9182

The CALGB 9182 trial used hydrocortisone, whereas both CCI-NOV22 and the trial by Berry et al. used prednisone. However both hydrocortisone and prednisone are forms of corticosteroid, both similar to a natural hormone produced by the adrenal

glands. They both relieve inflammation and are used to treat certain types of cancer. Both hydrocortisone and prednisone cause similar side effects such as stomach irritations, headaches and insomnia. In all three trials, the dosages of hydrocortisone and prednisone were equivalent and administered in the recommended manner.[18] Therefore, given these similarities, hydrocortisone and prednisone will be classed as equivalent corticosteroids.

Differences in the populations

In any meta-analysis and estimation of a pooled treatment effect, differences in the populations of the individual studies must be carefully considered. Trials can differ significantly especially with respect to patient selection and baseline characteristics. These differences may mean that combining the results from one trial conducted in a specific set of patients and the results from another trial conducted in a completely different patient population is inappropriate.

One of the key factors causing differences in the populations between trials is the varying inclusion criteria for each trial. The inclusion criteria for the trial by Berry et al. restricted eligibility to men with asymptomatic disease, CCI-NOV22 required patients to be symptomatic with symptoms including pain and disease progression, whereas CALGB 9182 required patients only to have metastatic disease – no restrictions on symptoms were imposed, meaning that this trial included a varied population – with both symptomatic and asymptomatic patients.

The impact of this means that the baseline characteristics and prognosis for patients in each of the trials may not be comparable and thus combining the results from each trial may be inappropriate. In particular, looking at the overall median survival of the patients in each trial, it looks like the patients in the trial by Berry et al. had longer life expectancies at baseline than the patients in CALGB 9182 and CCI-NOV22.

All of the patients included in the trial by Berry et al. were asymptomatic and 38% of patients included in CALGB 9182 had no analgesic requirement at baseline; however patients without pain and analgesic requirements were ineligible for inclusion in the CCI-NOV22 trial. Patients included in the trial by Berry et al. had better performance

status scores than those in CALGB 9182 and CCI-NOV22 at baseline; 99% of patients in the trial by Berry et al., 87% of patients in CALGB 9182 and 63% of patients in CCI-NOV22 had a performance status score of 0 or 1.

Patients had lower PSA levels at baseline in the trial by Berry et al. compared to CALGB 9182 and CCI-NOV22. The median baseline PSA levels for those receiving mitoxantrone was 56.7ng/ml, 209 ng/ml and 150 ng/ml respectively and for those receiving a corticosteroid median baseline PSA levels were 71.0ng/ml, 158 ng/ml and 141 ng/ml respectively. The number of prior treatments also varied between the studies – for example patients in CALGB 9182 had a greater prior exposure to antiandrogens compared to those in CCI-NOV22 (72% compared to 42%).

However, as all of the trials administered chemotherapy, all had to include men with mHRPC who were fit and healthy enough to receive chemotherapy. This means that the trials were conducted in a restricted subset of men with mHRPC who were healthy enough to receive such interventions. Thus the patient populations were reasonably comparable at baseline, and can be considered relatively homogeneous.

Results of the meta-analysis

Keeping in mind the various issues described in the previous section, we can present the following analysis.

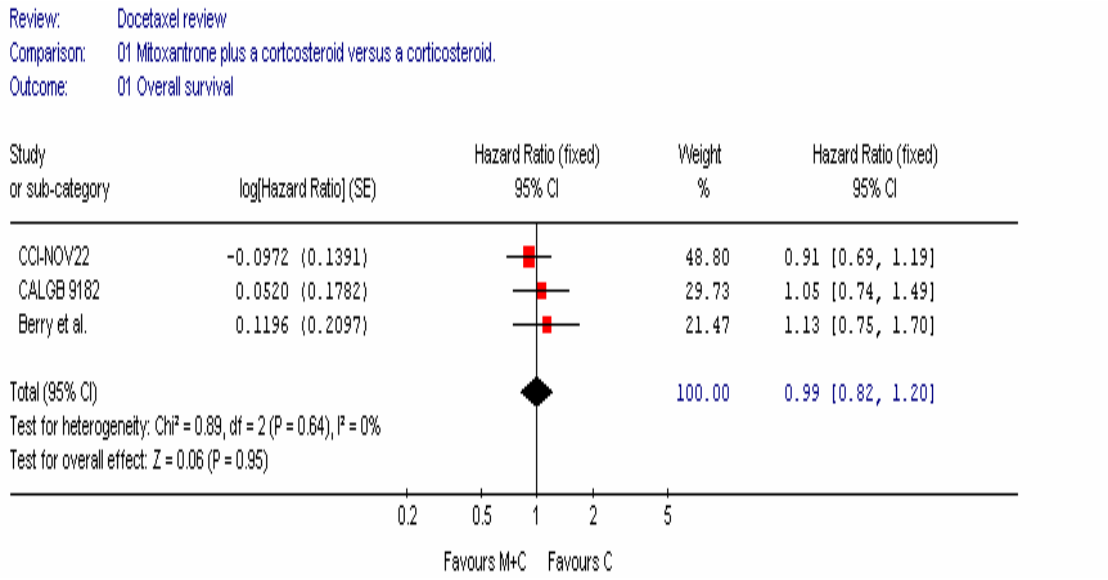
Overall survival

In order to obtain a pooled estimate of the effectiveness of a treatment with respect to time to event data such as overall survival, the most appropriate measures of effect to use are the hazard ratios and variances as calculated earlier.[25] We undertook a meta-analysis to obtain an overall estimate of the effectiveness of mitoxantrone plus a corticosteroid versus a corticosteroid with respect to overall survival.

The results of the meta-analysis suggest that mitoxantrone plus a corticosteroid has a similar effect on overall survival for men with mHRPC compared to a corticosteroid alone. The overall pooled estimate was very close to unity, and the 95% CIs included unity, therefore this finding was not of statistical significance. In fact the results show

that the effects of mitoxantrone plus corticosteroids and the effects of corticosteroids alone are almost the same. The results of the fixed effect meta-analysis are presented in Figure 4. Performing a random effects meta-analysis gave exactly the same estimate for the overall hazard ratio estimate and 95% CIs.

Figure 4. Pooled estimate of effectiveness of mitoxantrone plus a corticosteroid versus a corticosteroid - overall survival



From the above Forest plot, we can see from the test for heterogeneity that there is no statistically significant heterogeneity present between the three trials. However, the point estimates of the trials by Berry et al. and CALGB 9182 show a more favourable overall survival for the corticosteroid group compared to the mitoxantrone group, whereas the point estimate for CCI-NOV22 is going in the opposite direction and favouring mitoxantrone plus a corticosteroid.

The trials most comparable to TAX 327 in terms of treatment are CCI-NOV22 and the trial by Berry et al. as both of these trials administered prednisone instead of hydrocortisone. Crossovers were allowed in CCI-NOV22 as they were in TAX 327, meaning that these two trials are similar in that respect, and if CCI-NOV22 is the trial most comparable to TAX 327, the inclusion of crossovers may mean that the pooled estimate is actually a conservative one.

However, the trial most comparable to TAX 327 in terms of population is CALGB 9182, as this trial had both asymptomatic and symptomatic patients. The patient population eligible for inclusion in CCI-NOV22 had in general, a poorer prognosis than patients in TAX 327 and CALGB 9182, as this trial included only patients with pain related symptoms. The patients in the trial by Berry et al. had in general a better prognosis at baseline than any of the other trials as they were all asymptomatic.

Progression-free survival

It is not possible to perform a meta-analysis as the definitions of progression-free survival vary widely between the three trials.

Response rate

It is not possible to perform a meta-analysis as the definitions of response rate vary widely between the three trials.

Health-related quality of life

It is not possible to perform a meta-analysis as no data on quality of life were reported for the trial by Berry et al. and the definitions and instruments used to measure health-related quality of life vary widely between the other two trials. In addition, only 66% of patients in the CALGB 9182 trial were assessed at baseline and at least one follow-up, therefore this analysis is not true intention to treat. However, in the two studies that measured health-related quality of life, the mitoxantrone groups had statistically significant improvements compared with the corticosteroid groups. Due to the limited follow-up for this outcome these benefits should not be overstated.

Pain

It is not possible to perform a meta-analysis as no data on pain were reported for the trial by Berry et al. and the definitions and instruments used to measure pain vary between the two remaining trials. In addition, only 66% of patients in the CALGB 9182 trial were assessed at baseline and at least one follow-up, therefore this analysis is not true intention to treat. However, in the two studies that measured pain, the mitoxantrone groups had statistically significant improvements compared with the

corticosteroid groups. Due to the limited follow-up for this outcome these benefits should not be overstated.

PSA decline

It would be possible to obtain a pooled estimate for the relative risk of PSA decline, as all three trials have reported information on the proportion of patients who experienced a PSA reduction of at least 50% from baseline. However, PSA decline is not a very informative outcome in itself. As we have managed to obtain a pooled estimate for overall survival, it is unnecessary to obtain a pooled estimate for PSA decline.

Adverse effects of treatment

All three trials that assessed the effectiveness of mitoxantrone plus a corticosteroid versus a corticosteroid measured the adverse effects of treatment using the Toxicity Criteria from the National Cancer Institute. However various adverse effects of treatment were reported for each trial, limiting the opportunities to obtain pooled estimates for any single adverse effect of treatment. Also given the nature of adverse effects being specific to the interventions received, obtaining pooled estimates for the adverse effects of mitoxantrone plus a corticosteroid versus a corticosteroid has limited use in further indirect comparisons.

4.4.2. Comparison of all treatments versus mitoxantrone plus corticosteroids

In this chapter we present the median length of follow-up, the median survival and hazard ratio for overall survival for each identified trial. Each hazard ratio has been presented using mitoxantrone plus a corticosteroid as the common comparator. Only the results for overall survival have been presented, this is because the definitions and measurements of the other outcomes varied across the trials and thus it is impossible to make any comparisons between trials for any other outcome, as discussed previously. However, in the two studies comparing mitoxantrone plus a corticosteroid with a corticosteroid alone that measured health-related quality of life and pain responses (CCI-NOV22 and CALGB 9182), the mitoxantrone groups had statistically significant improvements compared with the corticosteroid groups. In addition, in the trial comparing mitoxantrone plus prednisone with docetaxel plus prednisone (TAX

327) 3-weekly docetaxel plus prednisone resulted in statistically significant improvements in terms of quality of life and pain compared with mitoxantrone plus prednisone. Therefore, it is not anticipated that the addition of these outcomes would change the conclusions based on the findings of this analysis.

The results are presented in Table 17.

Table 17. Overall survival comparisons with mitoxantrone plus a corticosteroid

Study	Median length of follow-up (Intervention)	Median length of follow-up (M+C)	Median Survival (Intervention)	Median Survival (M+C)	HR* (Intervention/M+C)	Lower 95% CI	Upper 95% CI
D+P (TAX 327 3w)[27]	20.8 months	20.7 months	18.9 months (17.0-21.2)	16.5 months (14.4-18.6)	0.76	0.62	0.94
D+P (TAX 327 1w)[27]	20.7 months	20.7 months	17.4 months (15.7-19.0)	16.5 months (14.4-18.6)	0.91	0.75	1.11
D+P+E (Oudard 70)[28]	Not stated	Not stated	18.6 months (95% CI: 14.9-22.3)	13.4 months (95% CI:9.4-17.5)	0.94	0.29	1.02
D+P+E (Oudard 35)[28]	Not stated	Not stated	18.4 months (95% CI: 14.1-22.8)	13.4 months (95% CI: 9.4-17.5)	0.86	0.68	1.08
D+E (SWOG 9916)[29]	32 months	32 months	17.5 months	15.6 months	0.8	0.67	0.97
P (Berry)[30]	21.8 months (range:2.4-50)	21.8 months (range:2.4-50)	23 months (range:3-49)	19 months (range:2-50)	0.89	0.59	1.34
P (CCI-NOV22)[31]	Not stated	Not stated	10 months	10 months	1.10	0.84	1.45
H (CALGB)[32]	Not stated	Not stated	12.6 months	12.3 months	0.95	0.67	1.35
M+P+Cl (Ernst)[33]	Not stated	Not stated	10.8 months (95% CI: 8.2-13)	11.5 months (95% CI: 8.8-14.4)	1.05	0.78	1.42
C (Pooled estimate)					1.01	0.83	1.22

D=Docetaxel, P=Prednisone/Prednisolone, E=Estramustine, H=Hydrocortisone, Cl= Clodronate, M=Mitoxantrone, C=Corticosteroid
*HR<1 favours Intervention.

From the data presented in this table it can be seen that only two treatments are statistically superior compared with mitoxantrone plus prednisone in terms of overall survival: 3-weekly docetaxel plus prednisone (HR=0.76 [95% CI: 0.62, 0.94]) and docetaxel plus estramustine (HR=0.80 [95% CI: 0.67, 0.97]). All other chemotherapy regimens, except mitoxantrone plus prednisone plus clodronate, show higher survival rates in comparison with mitoxantrone plus prednisone. However, the difference is not statistically significant. Mitoxantrone plus prednisone plus clodronate as well as corticosteroids alone show lower survival rates in comparison with mitoxantrone plus prednisone but, again, the difference is not statistically significant.

From these data it could be assumed that docetaxel plus prednisone is statistically superior compared with corticosteroids. The statistical significance of this comparison will be further explored in the next section (see chapter 4.4.3).

4.4.3. Docetaxel plus prednisone versus prednisone (indirect comparison)

Well designed randomised controlled trials are generally accepted as providing the most reliable evidence of the relative efficacy of two competing interventions.[62] However, two competing interventions of specific interest may not have been directly compared in randomised controlled trials. In such cases, it is possible to perform indirect comparisons if there is a 'common comparator' that links the interventions of interest. Undertaking simple indirect comparisons means that the power of randomisation is lost and data are subject to the biases associated with observational studies. An adjusted method for indirect comparisons has been proposed by Bucher et al.[63] which aims to overcome these potential problems. This method compares the treatment effect in different studies of different treatments relative to a common comparator, thus obtaining an unbiased estimate of the treatment effect of interest.

After performing a thorough search of the evidence available, there was only one trial (TAX 327) that compared docetaxel plus prednisone with another chemotherapy regimen and there were no trials available assessing the relative efficacy of docetaxel plus prednisone versus best supportive care. However, we did find trials comparing mitoxantrone plus a corticosteroid with one type of best supportive care: corticosteroids. Therefore, it was possible to perform an adjusted indirect comparison

to quantify the estimate of the relative efficacy of docetaxel plus prednisone versus corticosteroids. Empirical evidence presented by Song et al.[62] suggests that the results of adjusted indirect comparisons are not significantly different from those of direct comparisons.

However, it is important to take into account the problems associated with indirect comparisons. The internal and external validity of the trials included in the comparisons should be considered. A number of assumptions have to be made about the similarities of the trials involved in the indirect comparisons; in particular with regards to the patients included in the trials and the doses and schedules of interventions used. Because of these assumptions, the findings of any adjusted indirect comparisons should be interpreted with due caution.

In order to perform a formal indirect comparison between docetaxel plus prednisone versus corticosteroids, TAX 327 (which assessed docetaxel plus prednisone versus mitoxantrone plus prednisone) and the random effects pooled estimate for mitoxantrone plus corticosteroids versus corticosteroids obtained in 4.4.1 were compared. The random effects pooled estimate is recommended for use in this situation as using the fixed effect model can underestimate the standard errors of pooled estimates.[62] In using these trials, there are a number of differences between the studies which may limit the possibility of conducting an indirect comparison and its subsequent interpretation. Below the feasibility and issues of performing such an adjusted indirect comparison are discussed.

Differences between the pooled estimate and TAX 327

The internal validity and similarity of the trials evaluated in the indirect comparison should be carefully examined. In the case of using the pooled estimate obtained in chapter 4.4.1 and TAX 327, there are a number of differences and issues that may limit the interpretation of the adjusted indirect comparison. As discussed in chapter 4.4.1 there are several issues that were carefully considered before obtaining a pooled estimate for mitoxantrone plus a corticosteroid versus a corticosteroid. The issues discussed in this section are still clearly relevant and must be kept in mind when using the pooled estimate in any indirect comparisons.

Outcomes were measured differently in the trials

The primary outcome in TAX 327 was overall survival, with secondary outcomes of pain, PSA levels and quality of life. As discussed in chapter 4.4.1, differences in the definitions and measurements of outcomes preclude all indirect comparisons except overall survival.

The common comparator

In TAX 327, mitoxantrone plus prednisone was administered using a similar indication as the three trials used to obtain the pooled estimate in chapter 4.4.1. Therefore patients in all of the trials are receiving the 'common comparator' similarly. However, it still must be assumed that prednisone is equivalent to hydrocortisone in these circumstances.

Differences in populations

The trials used to obtain a pooled estimate in chapter 4.4.1 had varying inclusion criteria and therefore included patient populations with varying degrees of disease severity; from asymptomatic patients to patients experiencing pain with analgesic requirements. The inclusion criteria for TAX 327 restricted eligibility to those with progressive mHRPC. This means that this trial was conducted with a varied patient population which included both asymptomatic and symptomatic patients.

However, all patients included in the indirect comparison had to have progressive mHRPC to be eligible for inclusion. Thus the patient populations between trials can be regarded as a relatively homogeneous subset of patients healthy enough to receive chemotherapy. Also the adjusted indirect comparisons approach aims to obtain an unbiased estimate of treatment effect even if there are different prognostic characteristics between study participants in the trials included in the comparison.[62]

Results of the indirect comparison

Using the method proposed by Bucher et al.[63] and considering carefully the various restrictions and assumptions for performing adjusted indirect comparisons, we undertook an indirect comparison for overall survival only for the comparison of

docetaxel plus prednisone versus corticosteroids. Using the random effects pooled estimate for mitoxantrone plus corticosteroids versus corticosteroids derived in chapter 4.4.1, the estimated HR for death is 0.752 (95% CI: 0.567, 0.999). Full details of the calculations are presented in Appendix 10.8

The results of this adjusted indirect comparison suggest that docetaxel plus prednisone is superior to corticosteroids alone in improving overall survival. However, as the upper 95% CI is very close to unity, this finding is of borderline statistical significance.

As detailed in the previous chapter, CCI-NOV22 is perhaps the trial most comparable to TAX 327 in terms of treatment and the fact that crossovers were allowed in both, although the baseline prognostic factors of the patients in CCI-NOV22 were generally worse than those in TAX 327. However, one of the aims of using an adjusted indirect comparison approach is to reduce the possibility of bias introduced by any differences in prognostic characteristics between the populations included in the comparison.[62] This means that it is possible that the CCI-NOV22 is the most relevant and comparable trial within this adjusted indirect comparison.

Performing the indirect comparison again, using only the result from CCI-NOV22, we obtain an estimated HR for death of 0.689 (95% CI: 0.489, 0.972). This clearly shows that the initial estimated HR using the pooled treatment effect is more conservative**.**

For the adjusted indirect comparison to give an accurate estimate of the difference in treatment effect between competing interventions, a number of assumptions have to be made. Especially with regards to the similarities of the trials involved in the indirect comparisons; in particular the patients included in the trials and the doses and schedules of interventions used. Because of these assumptions, the findings of the adjusted indirect comparisons should be interpreted with due caution.

Indirect comparisons that do not include a comparison with docetaxel plus prednisone should not be undertaken, because the search strategy did not include searches for all available evidence that could inform such comparisons. Trials assessing the efficacy

of other chemotherapies or docetaxel in combination with any other treatment were not searched for, so there may be trials that could provide additional information if any further indirect comparisons were made. For the indirect comparison of docetaxel plus prednisone versus corticosteroids all available evidence that could inform the comparison has been included.

4.5. Summary of clinical effectiveness

We found one trial that assessed the intervention under consideration: docetaxel plus prednisone; this was in comparison with mitoxantrone plus prednisone (TAX 327). No other trials were found that assessed the clinical effectiveness of docetaxel plus prednisone. The results of this trial showed statistically significant improvements with 3-weekly docetaxel plus prednisone compared with mitoxantrone plus prednisone, in terms of overall survival, quality of life, pain response, and PSA decline. Response rate was higher for the 3-weekly docetaxel plus prednisone group than the mitoxantrone plus prednisone group, but this difference was not statistically significant. The improved outcomes for docetaxel plus prednisone were associated with more grade 3-4 adverse events; however, this had no detrimental effect on quality of life, which was also significantly improved in the 3-weekly docetaxel group. Progression-free survival was not assessed in this trial.

Since docetaxel plus prednisone is only compared with mitoxantrone plus prednisone, it was considered important to consider other evidence which would inform a comparison against other potentially relevant comparators (e.g. other chemotherapy-based treatments and best supportive care). Therefore, we searched for all other treatments that were compared with mitoxantrone plus a corticosteroid.

We found three trials comparing mitoxantrone plus prednisone with another chemotherapy regimen: one trial that compared mitoxantrone plus prednisone with docetaxel plus prednisone plus estramustine; one trial that compared mitoxantrone plus prednisone with docetaxel plus estramustine; and one trial that compared mitoxantrone plus prednisone with mitoxantrone plus prednisone plus clodronate. Both treatments that included docetaxel were superior to mitoxantrone plus prednisone in terms of overall survival (although the difference was not statistically

significant for docetaxel plus prednisone plus estramustine), response rate (although the difference was not statistically significant for docetaxel plus estramustine), and progression-free survival (although this was only assessed for docetaxel plus estramustine in comparison with mitoxantrone plus prednisone). Docetaxel plus estramustine was associated with more adverse events, compared with mitoxantrone plus prednisone. No significant differences were found between mitoxantrone plus prednisone plus clodronate and mitoxantrone plus prednisone without clodronate.

In addition, we found three trials that compared mitoxantrone plus a corticosteroid with best supportive care, i.e. corticosteroids. Two of these used prednisone (5 mg twice daily) as the comparator, while one compared mitoxantrone plus hydrocortisone with hydrocortisone (40 mg given in two divided doses daily). One of the trials included men with asymptomatic mHRPC; another included men with symptomatic mHRPC, with symptoms including pain and disease progression; while the third study included all men with progressive mHRPC. One trial allowed patients to cross over during the trial, this resulted in 50 out of 81 patients randomised to prednisone to receive additional mitoxantrone; the other two trials did not allow crossovers.

The combined result of these three trials showed very little difference between mitoxantrone plus corticosteroids compared with corticosteroids alone in terms of overall survival (HR=0.99 [95% CI: 0.82, 1.20]). Other outcomes could not be pooled because they were measured differently in the three trials. However, in the two studies that measured health-related quality of life and pain responses, the mitoxantrone groups had statistically significant improvements compared with the corticosteroid groups.

An adjusted indirect comparison was performed to estimate the relative efficacy of docetaxel plus prednisone versus corticosteroids. The results of the indirect comparison showed that docetaxel plus prednisone seems to be superior to prednisone alone in terms of overall survival. However, this is based on an indirect comparison using one good quality trial comparing docetaxel plus prednisone with mitoxantrone plus prednisone (TAX 327) and three trials comparing mitoxantrone plus corticosteroids with corticosteroids, that differed in terms of patient population and

methodology. Therefore, the results of this indirect comparison need to be interpreted with caution.

In summary, a direct comparison of docetaxel plus prednisone versus mitoxantrone plus prednisone in an open-label randomised trial showed statistically significant higher overall survival for docetaxel plus prednisone. Other outcomes, such as response rate, pain, and PSA decline were also in favour of docetaxel plus prednisone. These improved outcomes were associated with more grade 3-4 adverse events; however, this had no detrimental effect on quality of life, which was also significantly improved in the docetaxel plus prednisone group. Two other chemotherapy regimens were found that included docetaxel: docetaxel plus estramustine and docetaxel plus prednisone plus estramustine, both were superior to mitoxantrone plus prednisone in terms of overall survival, response rate, and progression-free survival. The only other chemotherapy regime we found that did not include docetaxel: mitoxantrone plus prednisone plus clodronate, showed no significant differences in comparison with mitoxantrone plus prednisone. Our review of the data suggests that docetaxel plus prednisone is the most effective treatment for men with mHRPC.

5. Economic review

5.1. Summary of studies included in the cost-effectiveness review

The systematic literature search detailed in Section 3.1 only identified one published study which met the criteria for inclusion in the cost-effectiveness review. In addition, a separate cost-effectiveness analysis was also submitted by Sanofi-Aventis.

The following sections provide a detailed overview of the cost-effectiveness evidence from each of these sources and an assessment of the quality and relevance of the data from the perspective of the UK NHS. Summary data extraction tables are reported for each review and the quality checklist for each study is reported in Appendix 10.9. An overall summary of the cost-effectiveness evidence is provided at the end of the chapter.

5.2. Published economic evaluations

Review of Bloomfield, D. et al (1998). Economic evaluation of chemotherapy with mitoxantrone plus prednisone for symptomatic hormone-resistant prostate cancer: Based on a Canadian randomized trial with palliative end points.[64]

Overview

The paper reports an analysis of the cost-effectiveness of mitoxantrone plus prednisone compared to prednisone alone. The evaluation was based on an analysis of patient-level data derived from prospective collection of resource use and patient outcome data from the CCI-NOV22 clinical trial.

The analysis of this Canadian trial was undertaken from the perspective of a third party payer (e.g. Provincial Ministry of Health). The primary outcome for the cost-effectiveness analysis was quality-adjusted life-years gained based on a comparison between the intervention groups. Mean total costs for each treatment were presented (comprising all inpatient and outpatient costs of hospital based resource use including drug acquisition costs, laboratory and diagnostic imaging costs, radiotherapy costs, costs of blood products and costs of surgery). In addition, due to the extent of the crossover within the trial, cumulative costs over time were presented for the two

treatment groups (as initially randomised) and for those in the prednisone group who did not crossover (intention to treat). Statistical techniques (Fieller's theorem) were used to determine a confidence interval for the incremental cost-effectiveness ratio (ICER) and deterministic sensitivity analyses were undertaken to assess the impact of variation in the costs.

A brief summary of the evaluation is provided in Table 18. The key features are described in more detail below.

Table 18: Summary of published study by Bloomfield et al. [64]

Author	Bloomfield et al.[64]
Date	1998
Type of economic evaluation	Cost-utility
Study classification	Patient level data II. Mixed prospective and retrospective data. (Type A: RCT)
Currency used	$ CAN plus conversion to $ US
Year to which costs apply	1996
Perspective used	3rd party payer (e.g. provincial ministry of health, insurance company or managed care plan)
Timeframe	Extrapolation to lifetime for costs and survival.
Comparators	(i) Mitoxantrone 12 mg/m^2 (every 3 weeks) plus 5 mg prednisone twice daily (ii) 5 mg prednisone twice daily
Source(s) of effectiveness data	CCI-NOV22
Source(s) of resource use data	CCI-NOV22 Retrospective chart review of a sample of trial patients (n= 114, 71%)
Source(s) of unit cost data	Costs for Ontario were applied: Admissions to cancer centre – Princess Margaret Hospital (PMH), Toronto (using hotel method) Other admissions – Ontario case cost project Outpatient costs – Ontario Health Insurance Plan (OHIP) fee schedule Laboratory tests and diagnostic imaging – OHIP fee schedule Chemotherapy costs – PMH Other drug costs – Ontario drug benefit formulary Radiotherapy – PMH + OHIP physician fee Blood products – Canadian Red Cross Surgery staff costs – OHIP
Modelling approach used	Analysis based on patient-level utility and resource use data from CCI-NOV 22
Summary of effectiveness results	Mean quality adjusted survival: Mitoxantrone plus prednisone = 41.5 weeks Prednisone = 28.2 weeks

	Difference = 13.3 weeks
Summary of cost results	Total per patient cost was estimated at $27,300 CDN for patients randomised to mitoxantrone plus prednisone (including $14,500 CDN for inpatient care, $4,300 CDN for chemotherapy and $1,400 CDN for analgesics) and $29,000 CDN for patients randomised to prednisone (including $19,100 CDN for inpatient care, $2,200 CDN for chemotherapy and $700 CDN for analgesics)
Summary of cost-effectiveness results	The baseline estimate showed that M+P dominated P with a cost-saving of $1,700 CDN and an additional 13.3 quality-adjusted weeks. The ICER associated with the upper 95% CI was $19,700 CDN per QALY gained (calculated using Fieller's theorem)
Sensitivity analysis	One-way sensitivity analyses were conducted by varying the total costs within each category over a plausible range (inpatient and outpatient +/- 25%, laboratory and diagnostic +/- 50%, surgery +/- 500%) and to the limits of the 95% CI. Only variation in the total cost associated with inpatient days caused M+P to become more costly than P

Summary of effectiveness data

Estimates of quality adjusted life years were based on patient level data from the CCI-NOV22 trial. Within the trial, patients completed the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 quality of life questionnaire every 3 weeks. The values for the global quality of life item were assumed to be equivalent to a rating scale and were converted to a 0-1 scale. In order to take account of the generally lower values assigned to quality of life from valuation schemes which do not incorporate risk (e.g. rating scales), these values were transformed to provide estimates of utility using a published transformation formula:

$$\text{Utility} = 1.07 * \text{rating scale value} \quad \text{when rating scale value} < 0.95$$
$$\text{Utility} = 1.00 * \text{rating scale value} \quad \text{when rating scale value} > 0.95$$

These utility values were then applied to the patient level survival data to generate patient level estimates of quality-adjusted survival. The patient level estimates were summated across each arm to generate mean total quality-adjusted survival for each treatment. No discounting was applied to the estimates of quality-adjusted survival due to the short nature of the follow-up.

Summary of resource utilisation and cost data

Resource use data for inpatient and outpatient hospital based resources were collected alongside the CCI-NOV22 clinical trial, via chart review, for a sample of patients (n=114/161) randomised to one of three Canadian centres. Other resource use incurred by the health care plan (e.g. visits to the family physician) was excluded, as was resource use external to the third party payer (e.g. incurred by patients and their families).

The inpatient and outpatient resource use was measured for different cost categories. These included inpatient care, outpatient clinic attendances, chemotherapy drug received, radiotherapy received, laboratory tests and diagnostic imaging received and surgery undertaken. Table 19 provides a breakdown of the importance of the individual cost categories as a percentage of the overall cost for each treatment (taken from Bloomfield et al).[64]

Table 19: Percentage of costs by resource category

	Percentage of total cost	
Category	**M+P**	**P**
Inpatient	53.0	65.8
Outpatient	10.3	8.3
Chemotherapy drug	11.2	5.1
Chemotherapy administration	4.5	2.3
Radiation	4.2	4.3
Analgesic medication	5.0	2.4
Prostate-related drug	4.1	2.8
Diagnostic	3.0	4.0
Blood products	1.0	1.3
Biochemistry	1.2	1.1
Haematology	1.1	1.0
Surgery	0.3	0.6
General drugs	0.3	0.2
Blood-product related	0.3	0.2

Cardiac	0.3	0.1
Antibiotics	0.2	0.2
Microbiology	0.2	0.1

Inpatient, outpatient and radiation therapy costs were estimated by applying hotel costs (derived from the Princess Margaret Hospital (PMH) in Toronto) to the individual patient level resource use. The hotel costs covered nursing, laundry, food and overheads. The cost of physician services and investigations were estimated from the Ontario Health Insurance Plan (OHIP) fee schedule. The acquisition costs associated with chemotherapy drugs (mitoxantrone) and intravenous antibiotics were taken from the PMH pharmacy. Other inpatient drugs were not included as their use was low. Outpatient drugs were costed via the Ontario Drug Benefit Formulary. All costs were presented in terms of 1996 CDN $. No discounting was applied to costs due to the short nature of the follow-up.

The individual elements of cost were summated for each patient to provide patient level data on total cost, from which treatment specific total costs were estimated. In addition, mean cumulative costs were presented as a function of time for each treatment (according to initial randomisation) and for the patients randomised to and remaining on prednisone. This allowed investigation of the issue of crossover within the trial. At an individual patient level, these plots illustrated a common pattern with low costs initially followed by a steep rise towards the end of life. At the treatment level, the curves were separated but there was no statistically significant difference in the cumulative costs over time.

Summary of cost-effectiveness analysis

The results of the cost-effectiveness analysis were presented in terms of the incremental cost per quality-adjusted life-year gained. The baseline estimate of the cost-effectiveness indicated that the use of M+P dominated P - with an additional 13.3 quality-adjusted weeks and a reduced cost of CDN $1,700.

Fieller's theorem was used to calculate the confidence interval for the ICER. The upper 95% confidence limit for the ICER was estimated as CDN $19,700 per QALY gained.

The results for the ICER analysis are reported in Table 20.

Table 20: Cost-effectiveness summary

Intervention	Mean Costs	Mean quality-adjusted weeks	ICER
M+P	CDN $27,300	41.5	
P	CDN $29,000	28.2	
Incremental	- CDN $1,700	13.3	M+P dominates P

Limited sensitivity analyses were undertaken in order to assess the robustness of the results to variation in the costs. A one-way, deterministic sensitivity analysis was undertaken for the mean total cost of each category over the following ranges: inpatient and outpatient costs +/- 25%, laboratory and diagnostic costs +/- 50% and surgery costs +/- 500%. M+P remained cost-saving for all of the analyses. A further one-way sensitivity analysis was undertaken for the costs in each category, with the total costs varied within the 95% confidence interval to favour each treatment individually. M+P remained cost-saving except in the face of variation in the total cost of inpatient days. Specific results were not reported.

Comments

The economic analysis is based on patient-level data from CCI-NOV22, and as such the results are likely to have good internal validity. However, the study does suffer from some potential limitations which affect its applicability for health-care decision-making within the NHS. Firstly, it is unclear how generalisable the results are to the NHS setting. The study was undertaken in Canada using Canadian practice patterns and the authors suggest that the results should only be generalised to similar healthcare systems. In addition, the report presents total costs per category with no separation between the unit costs and resource use. This further limits the transfer of the results to NHS practice. Secondly, the analysis undertaken within the study only

considers the comparison of mitoxantrone plus prednisone with prednisone/prednisolone alone. Therefore the analysis ignores other chemotherapies that are potentially relevant to the NHS (i.e. docetaxel and estramustine). Finally, the valuation of benefit undertaken within the analysis involved translating measures of quality of life obtained from patient completed questionnaires into a proxy rating scale and then to utilities via a published formula. This does not conform to the requirements of the NICE reference case which recommend societal valuations obtained using a standardised and validated generic instrument.

5.3. Company submissions

Review of Sanofi-Aventis (2005). Sponsor submission to the National Institute for Health and Clinical Excellence: Taxotore® (docetaxel) in Metastatic Hormone-refractory Prostate Cancer (mHRPC).[61]

Overview

The economic analysis in the submission by Sanofi-Aventis evaluated the cost-effectiveness of docetaxel plus prednisone (3-weekly regimen) compared to mitoxantrone plus prednisone. The evaluation was based on an analysis of patient-level data derived from prospective collection of resource use and patient outcome data from the TAX 327 clinical trial. Although TAX 327 included two alternative docetaxel regimens (3-weekly and weekly administration), only the 3-weekly regimen was considered in the cost-effectiveness analysis due to current licensing.

The analysis was undertaken from an NHS perspective. Overall costs were separated into 2-main elements: the *first-line chemotherapy phase* (comprising the drug acquisition costs, costs of administration and hospitalisations for adverse events) and the *follow-up phase* (including subsequent chemotherapy, palliative therapies and hospitalisations). The primary outcome for the cost-effectiveness analysis was life-years gained based on a comparison of overall survival in the different intervention groups. Separate life-years gained estimates were provided based on a within-trial comparison (using median survival data) and a lifetime comparison (using mean survival data). The lifetime comparison was based on an extrapolation approach using

parametric survival-analysis. Decision uncertainty was assessed using simple deterministic sensitivity analysis.

A brief summary of the evaluation is provided in Table 21. The key features are described in more detail below.

Table 21: Summary of submission by Sanofi-Aventis

Author	Sanofi-Aventis [61]
Date	2005
Type of economic evaluation	Cost-effectiveness
Study classification	Patient level data I.Prospective resource use and patient outcome data (Type A: RCT)
Currency used	UK Pounds sterling
Year to which costs apply	A unique price year was not given
Perspective used	UK NHS
Timeframe	Within trial analysis and extrapolation to lifetime (survival only)
Comparators	(i) Docetaxel 75 mg/m^2 plus prednisone (every 3 weeks) (ii) Mitoxantrone 12 mg/m^2 plus prednisone (every 3 weeks)
Source(s) of effectiveness data	TAX 327
Source(s) of resource use data	TAX 327
Source(s) of unit cost data	Not stated
Modelling approach used	Analysis based on patient-level survival and resource use data from TAX 327. Separate analyses conducted for within trial analysis and life-time horizon using parametric survival analysis (Weibull distribution) to extrapolate survival data
Summary of effectiveness results	Median survival from Kaplan-Meier: Docetaxel plus prednisone =18.9 months Mitoxantrone plus prednisone =16.5 months *Difference = 2.4 months* Mean survival based on extrapolation using parametric survival model using Weibull distribution (95% CI): Docetaxel = 22.38 (20.38-24.62) months Mitoxantrone = 18.65 (17.30 – 20.12) months *Difference=3.73 months*
Summary of cost results	Total per patient cost was estimated at £15,767 for docetaxel plus prednisone (comprising £8,329 for first-line chemotherapy and £7,438 for further therapy) and £9,711 for mitoxantrone plus prednisone (comprising £1,695 for first-line chemotherapy and £8,016 for further therapy)
Summary of cost-effectiveness results	The incremental cost per life-year gained for docetaxel was £30,280 based on median survival data. Using mean survival,

	estimated using parametric survival methods, the incremental cost per life-year gained for docetaxel was reported to be £19,483
Sensitivity analysis	One-way sensitivity analyses were conducted by varying the mean survival difference based on the lower and upper bounds estimated for docetaxel plus prednisone. The ICER ranged from £12,173 to £42,007 per life-year gained

Summary of effectiveness data

Survival estimates were based on patient-level data from the TAX 327 trial. Two separate analyses were undertaken: 1) *a within-trial analysis* - using median survival estimates, and 2) *a lifetime analysis* - based on mean survival duration. In order to estimate mean survival duration it is necessary to estimate the area under the entire survival curve. In situations in which censoring exists, the survival curves must be extrapolated beyond the observed data to eliminate right censoring. Consequently, a parametric survival model was fitted in order to obtain an estimate of mean survival duration for each of the two interventions.

A Weibull model was applied to the survival data based on a visual check of a plot of log-cumulative hazard against log time. A Weibull model is used in situations in which the assumption of a constant hazard with respect to time is not appropriate (i.e. the risk of mortality is increasing/decreasing). Survival analysis was undertaken using PROC LIFEREG in SAS (v9.1). The mean survival was estimated from the output parameters (intercept and scale) using the following formula:

$$\text{Mean survival} = \exp\{\text{intercept}\} \times \Gamma(\mathbf{1} + \text{scale parameter})$$

Table 22 provides a comparison of the alternative analyses based on the different approaches. The results demonstrate that the within-trial analysis, based on median survival (based on the Kaplan-Meier analysis), results in a more conservative estimate of the difference between the interventions (2.4 months) compared to the estimate based on mean survival (3.73 months). While the mean survival estimate is considered more appropriate for the purposes of the cost-effectiveness analysis, the difference between these estimates demonstrates that uncertainty surrounding the estimates should be appropriately considered in the final results. No discounting was applied to these estimates.

Table 22: Comparison of survival estimates based on within trial analysis and extrapolation approaches

	Results from parametric survival analysis			Within-trial analysis
Treatment	Intercept	Scale	Mean Survival (months)	Median Survival (months)
Docetaxel	3.214	0.6482	22.38 (20.38-24.62)	18.9
Mitoxantrone	3.036	0.6184	18.65 (17.30-20.12)	16.5
Difference			3.73	2.40

Summary of resource utilisation and cost data

Resource utilisation and cost data were estimated for both the first-line chemotherapy phase and subsequent costs incurred during the follow-up period. Resource use data collected alongside the TAX 327 clinical trial were costed using UK unit costs in order to estimate average per patient costs. The costs of drug and administration were presented separately from other in-trial costs that were incurred during the first-line chemotherapy phase (i.e. the costs of managing side-effects) and those that accrued during the follow-up phase. Hospitalisations due to the management of side-effects were not reported separately from hospitalisations due to other reasons (e.g. palliative care). No discounting was applied to costs.

The drug and administration costs are summarised in Table 23.

Table 23: Total costs of first-line chemotherapy phase (drug and administration costs)

	Docetaxel (3-weekly regimen)		Mitoxantrone	
	Docetaxel	Prednisone	Mitoxantrone	Prednisone
Dose per cycle (mg/m^2)	75	10	12	10
Mean body surface area (m^2)	1.7		1.7	
Total dose per cycle (mg)	127.5	210	20.4	210
Cost per cycle	£1,023	£1.02	£169.25	£1.02
Total drug cost per cycle	£1,024		£170	
Administration cost per cycle	117		117	
Mean no. of cycles	7.3		5.9	
Total cost (drug and administration)	£8,329		£1,695	

The total drug and administration costs were based on the protocol doses stated in TAX 327 (e.g. 75 mg/m^2 for docetaxel and 12 mg/m^2 for mitoxantrone). This appears to be a conservative approach since no adjustments were made for dose-reduction for patients experiencing side-effects on either chemotherapy regimen. However, no costs were allocated to the use of pre-medication (oral dexamethasone) for patients receiving the docetaxel 3-weekly regimen. The exclusion of these costs is unlikely to significantly alter the results due to the low-acquisition cost associated with pre-medication (estimated to be approximately £5.94 per cycle).

To estimate the total drug costs incurred per cycle, the protocol doses were adjusted by a mean body surface area of 1.7m^2. No supporting reference for this body surface area was provided in the main sponsor submission. After requesting further clarification from Sanofi-Aventis, this estimate was stated to be 'common practice'.

In the review of clinical effectiveness data, only one trial was identified that reported body surface area. CCI-NOV22 reported a mean body surface area of 1.9m^2 in each of the trial arms. This corresponds exactly to the normal values reported for males in the general population.[65] Consequently, assuming a body surface area of 1.7m^2 may underestimate the total costs for both docetaxel and mitoxantrone for this population, depending on whether an additional vial (or larger vial size) is required to administer the required dosage for this higher body surface area. The potential implications of this are addressed in the commentary section.

Administration costs were reported to be £117 per cycle. No supporting reference was provided to the source of this unit cost. After consultation with Sanofi-Aventis the figure was stated to be based on the ISDScotland cost book which classifies oncology speciality treatment as radiotherapy. Hence it has been assumed that the cost of chemotherapy administration is costed as a radiotherapy outpatient visit which is listed as £117 (based on 2002/2003 prices).

The number of cycles of chemotherapy applied in this analysis was based on the mean number of cycles derived from TAX 327. While from an economic perspective it can be argued that the mean is the most appropriate measure of central tendency from a decision-maker's perspective, a comparison of these estimates with the median number of cycles suggests that the distribution of chemotherapy cycles is highly skewed. The median number of cycles (range) reported in TAX 327 were 9.5 (1 to 11) for the docetaxel 3-weekly regimen and 5 (1 to 11) for mitoxantrone. Hence, the analysis based on mean number of cycles (7.3 vs 5.9) will result in lower average costs for the docetaxel regimen and higher costs for mitoxantrone in comparison with an analysis based on median number of cycles. In these instances, while the mean may be considered the most appropriate point estimate, it is important to demonstrate the robustness of the results to alternative assumptions due to the relatively high uncertainty surrounding these point estimates. This issue is discussed further in the commentary section.

Table 24 summarises the other in-trial costs including the costs of managing side-effects during first-line chemotherapy phase and costs incurred during follow-up

phase. Mean total costs were approximately £579 lower in the docetaxel group compared to patients randomised to receive mitoxantrone. Much of this difference was attributed to a reduction in the cost of subsequent chemotherapy and lower hospitalisation costs.

Table 24: Other in-trial costs

Item	Docetaxel	Mitoxantrone	Difference* (Doc – Mitox)
Blood	£14	£12	£3
Bisphosphonates	£317	£264	£53
Epoetin	£84	£27	£59
G-CSF	£96	£12	£84
Hormone therapy	£1,661	£1,265	£396
Chemotherapy	£2,710	£3,381	-£671
Hospitalisations	£2,555	£3,056	-£501
Total	£7,438	£8,016	-£579

* Rounded to 2 decimal places

The mean total costs of first-line chemotherapy and follow-up costs are summarised in Table 25. Total costs were approximately £6,056 higher for patients randomised to receive docetaxel compared to mitoxantrone. The majority of this difference was attributed to the higher drug acquisition costs of docetaxel. Although subsequent follow-up costs were lower in this group, these differences were more than offset by these higher initial costs.

Table 25: Total cost of treatment per patient

	Docetaxel	Mitoxantrone	Difference* (Doc – Mitox)
First-line chemotherapy	£8,329	£1,695	£6,634
Follow-up costs	£7,438	£8,016	-£579
Total	£15,767	£9,711	£6,056

* Rounded to 2 decimal places

While formal survival analytic approaches have been applied to account for censoring in the survival data, it is unclear how censoring in the cost data has been accounted for in these analyses. The total costs presented in the report are described as "generating an average lifetime cost per patient" (p53).[61, 66-68] However, no details were provided in order to ascertain the validity of the approach used to handle censoring in the cost data.

A separate sensitivity analysis was, however, undertaken using the method proposed by Lin et al, for estimating average costs in the presence of censoring.[69] The method by Lin et al requires the time period of interest to be partitioned into a number of separate small intervals and then the Kaplan-Meier estimate for the probability of dying in each interval is multiplied by the sample mean of the total costs from the observed deaths in that interval. In accordance with this approach, the follow-up period was divided into 8 time intervals: 0-6 months (based on the period over which the randomised intervention was planned) and then at four-monthly intervals. Using this approach the mean total costs (including first-line chemotherapy and follow-up costs) were estimated to be £15,578 for docetaxel and £10,028 for mitoxantrone, a difference of £5,550. Although this difference does not appear to be substantially different to those reported in the base-case analysis (£5,550 compared to £6,056) it is difficult to assess which is more robust due to the lack of transparency in the methods used in the main analysis.

Summary of cost-effectiveness analysis

Results of the cost-effectiveness analysis were presented in terms of the incremental cost per life-year gained. Separate ICERs were presented based on the within-trial analysis (based on median survival) and the extrapolation model (based on mean survival estimates). Results based on median survival were stated to be preliminary results and the results based on mean survival were taken to be the base-case analysis. Additional sensitivity analyses were only conducted on the base-case scenario.

Table 26 summarises the ICER for the 2 separate analyses. Based on the within-trial analysis, the ICER was £30,380 per life-year gained. Using mean survival from the extrapolation model improved the ICER to £19,483 per life-year gained.

Health utility estimates were not collected as part of TAX 327 and no estimates of the incremental cost per quality-adjusted life year were provided. The submission stated that after reviewing available external evidence (details not reported in the submission), the existing values identified were inconsistent and hence were not considered sufficiently robust to be used in conjunction with the results presented in the main analysis.

Table 26: Cost-effectiveness summary

Analysis	Intervention	Mean Costs	Mean LYG	ICER
Within trial	Docetaxel	£15,767	1.575	£30,280
	Mitoxantrone	£9,711	1.375	NA
Extrapolation	Docetaxel	£15,767	1.865	£19,483
	Mitoxantrone	£9,711	1.554	NA

Only limited sensitivity analyses were undertaken in order to assess the robustness of these results. A one-way, deterministic sensitivity analysis was undertaken using the estimates of the lower and upper bound (95% CI) for mean survival for the docetaxel 3-weekly regimen, while keeping the mean survival estimate for mitoxantrone constant. The cost per life-year gained ranged from £12,173 (upper bound) to £42,007 (lower bound).

Comments

Overall this appears to be a reasonable evaluation. The analysis is based on a patient-level analysis of TAX-327 (and UK specific cost data), and as such the results are likely to have good internal and external validity. In addition, the approach to estimating mean survival, based on the extrapolation of survival data, appears robust and is necessary in order to quantify the potential lifetime consequences of the different interventions. However, the ICER does appear to be potentially sensitive to the time-horizon and demonstrates that the assumption that benefits are maintained over a longer-time horizon may be an important assumption in relation the potential cost-effectiveness of docetaxel plus prednisone.

The study does, however, suffer from several potential limitations. Some of these are simply due to a lack of transparency regarding some of the assumptions applied to the costs of the first-line chemotherapy phase and also the main approach used to handle censoring in the cost data. In order to address the first of these potential limitations we have conducted two additional sensitivity analyses to examine the robustness of the base-case results to a reasonable set of alternative assumptions. In particular, in the review of resource utilisation and costs, we noted that a higher mean body surface area of $1.9m^2$ should be applied to each of the trial arms. This figure represents the only value reported in the clinical trials considered and corresponds with normal values reported for males in the general population. In addition, we reported that the analysis had not included the additional pre-medication costs associated with the use of oral dexamethasone for patients receiving docetaxel based regimens. We also highlighted that the robustness of the results to variation in the number of cycles should be considered, due to the marked skewness in this distribution. As an alternative scenario we have applied the median number of cycles reported in TAX 327. We explore the robustness of the base-case model to these revised assumptions using two separate analyses:

- *Revised Analysis 1* - a revised body surface area of $1.9m^2$ was assumed and the additional costs of pre-medication of oral dexamethasone were applied.
- *Revised Analysis 2* – as above but also replacing the mean number of cycles with the median number of cycles.

The results of these additional sensitivity analyses are presented in Table 27. Applying a higher body surface area and including the additional costs of pre-medication does not appear to have much of an impact on the overall results. However, the application of median (as opposed to mean) number of cycles has a more marked impact on the ICER, increasing from £30,283 to £46,095 per life-year gained in the within-trial analysis and from £19,483 to £29,659 in the lifetime analysis. This demonstrates that the results are potentially sensitive to the assumption related to the number of cycles and clearly illustrate it is important to quantify this appropriately in order to reflect the resulting decision uncertainty.

Table 27: Cost-effectiveness results based on revised assumptions

Revised Analysis 1				
Analysis	**Intervention**	**Mean Costs**	**Mean LYG**	**ICER**
Within trial	Docetaxel	£16,168	1.575	£32,285
	Mitoxantrone	£9,711	1.375	NA
Extrapolation	Docetaxel	£16,168	1.865	£20,773
	Mitoxantrone	£9,711	1.554	NA
Revised Analysis 2				
Analysis	**Intervention**	**Mean Costs**	**Mean LYG**	**ICER**
Within trial	Docetaxel	£18,776	1.575	£46,095
	Mitoxantrone	£9,557	1.375	NA
Extrapolation	Docetaxel	£18,776	1.865	£29,659
	Mitoxantrone	£9,557	1.554	NA

The methods used to assess the robustness of the base-case results to parameter uncertainty are extremely limited and are confined to a one-way sensitivity analysis of survival data. The report states that a probabilistic analysis was not undertaken since "it was felt that the assumptions required to characterise the variation in most variables was too high to make this approach robust" (p55).[61] It could equally be argued that it is precisely these situations (e.g. situations with high parameter uncertainty) when it is most critical to appropriately characterise uncertainty and to reflect the resulting decision uncertainty. Consequently, it is not possible to assess the robustness of the results to the uncertainty surrounding other parameters.

Finally, an important omission from the current analysis is the lack of adjustment for the quality of life of this patient group and also the potential impact of toxicities/palliative benefits has not been considered in this analysis. Ideally, a generic measure of health outcomes (e.g. quality-adjusted life-years [QALYs]) should be used to enable the cost-effectiveness results to be compared to other interventions in different disease areas. Although the submission stated that a review of available literature was conducted, specific details were not reported so it is difficult to assess the potential inconsistency described in the submission. Despite any potential

inconsistencies it would seem important to assess the robustness of the results based on different assumptions pertaining to the quality of life of this patient group.

5.4. Summary of findings from the cost-effectiveness review

The review of economic evidence from the literature and industry submission has highlighted a number of potential limitations for the purposes of informing a decision from the perspective of the NHS. Perhaps the most significant limitation of the available evidence is that neither of these studies directly compares the full range of possible strategies that are potentially relevant to the NHS (i.e. docetaxel, mitoxantrone, estramustine, best supportive care etc). Consequently it is not possible to make any direct comparison of the relative cost-effectiveness of these alternative treatments from this evidence. This is a major issue since the main comparator in the submission by Sanofi-Aventis is not currently licensed in the UK for HRPC, although it does appear to be widely used in the UK for this indication. In these instances it is important to assess the cost-effectiveness of docetaxel plus prednisone in relation to all relevant comparators.

One possible conclusion that might be drawn from the two separate studies is that since mitoxantrone plus prednisone dominated prednisone in the study by Bloomfield, a comparison of the ICER between docetaxel plus prednisone and mitoxantrone plus prednisone reported in the submission by Sanofi-Aventis is likely to be the most informative comparison. However, there are a number of potential caveats to this conclusion. Firstly, the quality of life associated with mHRPC has not been adequately reflected in the submission by Sanofi-Aventis. Secondly, the approaches used for handling uncertainty in the submission were limited and did not consider the full range of uncertainties in the input parameters applied in the evaluation. Finally, even if it is anticipated that an intervention is likely to be dominated, based on expected costs and outcomes, it will still be important to include this comparator within the analysis in order to appropriately reflect decision uncertainty.

In summary, the existing evidence relating to the cost-effectiveness of docetaxel plus prednisone for men with mHRPC has a number of limitations which make the current evidence base insufficient to inform decision making regarding the most appropriate

treatment for men treated in England and Wales. The following chapter therefore presents a new decision analytic model that has been developed to address a number of these issues more formally. Central to this new model is the need to facilitate a direct comparison between the different comparators.

6. Economic model

6.1. Introduction

The review of cost-effectiveness studies in Section 5 identified a number of important limitations in the existing studies for assessing the cost-effectiveness of docetaxel plus prednisone/prednisolone for advanced mHRPC. In particular, no existing study has attempted to compare the full range of relevant treatment strategies from the perspective of the NHS. In addition, there are currently no estimates reporting on the potential incremental cost-per quality adjusted life year for docetaxel plus prednisone/prednisolone in relation to other chemotherapy based regimens or palliative care options. To address these limitations and to facilitate a direct comparison of the relative cost-effectiveness of all relevant comparators, a new decision analytic model was developed. This model provides a framework for the synthesis of data from the clinical effectiveness and economic reviews in order to develop a single, coherent analysis of the main comparators identified. The following sections outline the structure of the model in detail and provide an overview of the key assumptions and data sources used to populate the model.

6.2. Methods

Overview

The model has been developed to estimate costs from the perspective of the UK NHS and health outcomes in terms of life-years gained (LYG) and quality-adjusted life-years (QALYs) for the full range of relevant treatment strategies. A lifetime time horizon has been used.

The model is probabilistic in that input parameters are entered into the model as probability distributions to reflect 2nd order uncertainty – that is, uncertainty in the mean estimates.[70] Monte Carlo simulation is used to propagate uncertainty in input parameters through the model in such a way that the results of the analysis can also be presented with their uncertainty**.** A 2003-2004 price base is used, and a discount rate of 3.5% per annum is applied to costs and health outcomes.

Treatment strategies under comparison

Two separate analyses have been conducted. The first extends the comparators considered in the submission by Sanofi-Aventis to include "best supportive care" (modelled using prednisone/prednisolone alone). This analysis examines the incremental cost-effectiveness and decision-uncertainty for a comparison of docetaxel plus prednisone/prednisolone (3-weekly regimen), mitoxantrone plus prednisone/prednisolone and prednisone/prednisolone alone. The second analysis extends this comparison to include the full range of potential comparators identified in the clinical effectiveness review.

In the first analysis, 3 strategies are considered:

- **D+P (3-weekly)**: Docetaxel (75 mg/m^2 every 3 weeks) plus prednisone/prednisolone (5 mg orally twice daily);
- **M+P**: Mitoxantrone (12 mg/m^2 every 3 weeks) plus prednisone/prednisolone (5 mg orally twice daily);
- **P**: Prednisone/prednisolone (5 mg orally twice daily).

In the second analysis, 8 strategies are considered; comprising the 3 strategies considered in the first analysis and the following 5 additional strategies:

- **D+P (weekly)**: Docetaxel (30 mg/m^2 on days 1, 8, 15, 22 and 29 in a 6-week cycle) plus prednisone/prednisolone (5 mg orally twice daily);
- **D+E**: Docetaxel (60-70 mg/m^2 every 3 weeks) plus estramustine (three times daily on days 1-5);
- **D+E+P (70)**: Docetaxel (70 mg/m^2 every 3 weeks) plus estramustine (840 mg in 3 divided doses on days 1 to 5 and 8 to 12) plus prednisone/prednisolone (5 mg orally twice daily);
- **D+E+P (35)**: Docetaxel (35 mg/m^2 twice every 3 weeks) plus estramustine (840 mg in 3 divided doses on days 1 to 5 and 8 to 12) plus prednisone/prednisolone (5 mg orally twice daily);
- **M+P+C**: Mitoxantrone (12 mg/m^2 every 3 weeks) plus prednisone/prednisolone (5 mg orally twice daily) plus clodronate (1,500 mg over 3 hours every 21 days).

We have presented the results using two separate analyses to reflect the unlicensed status of the majority of comparators considered in the second analysis. The second analysis ensures that the complete range of potential comparators identified in the clinical effectiveness review is evaluated in the economic analysis. However, since docetaxel (75 mg/m^2 every 3 weeks) is only currently licensed in combination with prednisone/prednisolone (5 mg orally twice daily) for HRPC, we believe that presenting these as separate analyses enables the decision maker to determine whether these additional comparators are considered relevant from their perspective. In this context, the choice of appropriate comparators is considered to be a form of structural uncertainty and therefore is modelled using separate analyses. This approach also facilitates a comparison of the alternative analyses and ensures that decision uncertainty can be appropriately characterised depending on the range of comparators included in the analysis.

6.3. Model structure and parameter inputs

Survival

Given the inconsistencies in the definitions and the measurements of outcomes across the trials considered in the clinical-effectiveness review, the model focuses on overall survival as the primary outcome. From an economic perspective, the advantage of using overall survival is that is represents a final outcome as opposed to an intermediate outcome (e.g. PSA response, progression-free survival etc). As such, this provides a direct link to the main outcome used in the cost-effectiveness analysis: quality-adjusted life years (QALYs). In addition, this approach provides consistency between the clinical-effectiveness review and economic model, ensuring that the approaches to evidence synthesis are undertaken in a unified manner.

A simple 2-state (alive/dead) Markov model was constructed to calculate mean survival and to account for discounting.[71] Transition probabilities to the dead state were based on a cycle length of one month. The model was run for a time horizon of 15-years (based on a starting age of approximately 68 years as reported in TAX 327) in order to obtain a robust estimate of mean survival.

Transitions for the three comparators reported in TAX 327, (D+P (3-weekly), M+P and D+P (weekly), were modelled using the results from the Weibull model reported in the submission by Sanofi-Aventis. Formally, the Weibull distribution has the following probability density function:

$$f(t) = \lambda\gamma t^{\gamma-1} \exp\{-\lambda t\gamma\}$$

This function is characterised by two parameters λ and γ .

The hazard function for this distribution is:

$$h(t) = \lambda\gamma t^{\gamma-1}$$

In the case of $\gamma = 1$, the Weibull expressions above reduce to those of the exponential distribution (i.e. the hazard is constant with respect to time).

For the purposes of the economic model, the hazard function was modelled using the parameters λ and γ . The submission by Sanofi-Aventis presented the results of the Weibull model based on the intercept and scale parameters from the output of a parametric survival analysis undertaken using PROC LIFEREG in SAS (v9.1). In terms of the hazard function reported for the Weibull distribution, the intercept and scale parameters from this output can be expressed in terms of the two parameters λ and γ ; where λ = EXP(-Intercept/Scale) and γ = 1/scale. The intercept and scale parameters reported in the submission by Sanofi-Aventis were used as the basis in which to model the hazard for the different interventions.

As previously stated in the economic review section, the submission by Sanofi-Aventis presented the mean estimate for the coefficients for the intercept and scale parameters for two interventions: D+P (3-weekly) and M+P. Since this analysis was based on a patient-level analysis of survival data from the TAX 327 study, it was decided that this approach would provide the most reliable approach to quantifying mean survival for these interventions. Additional data were therefore requested in order to extend the approach used by Sanofi-Aventis to facilitate the inclusion of

other relevant comparators and to ensure that uncertainty surrounding the coefficients was incorporated in the final decision model. Furthermore, the use of the Markov model to estimate mean survival enabled discounting to be incorporated. Details of the intercept and scale parameters for the D+P (weekly) arm of TAX 327 were requested in addition to the standard errors for these coefficients for each of the three comparators in this trial. Details of the information reported in the economic review are reported alongside the additional information provided on request from Sanofi-Aventis in Table 28.

Table 28: Regression coefficients from Weibull model

Treatment	**Intercept Mean (SE)**	**Scale Mean (SE)**
D+P (3-weekly)	3.214 (0.0546)	0.6482 (0.0438)
D+P (weekly)	3.078 (0.0447)	0.597 (0.0368)
M+P	3.036 (0.0447)	0.6184 (0.0371)

For the purposes of the probabilistic analysis it is also important to reflect the covariance between the intercept and scale parameters from the Weibull regression. The covariance matrix for each intervention was supplied on request by Sanofi-Aventis. This matrix was used to derive the Cholesky decomposition matrix which was then used to allow for correlation when generating the random normal draws for the intercept and scale parameters in the probabilistic simulation.[72] The covariance matrix and associated Cholesky decomposition matrix are reported in Table 29.

Table 29: Covariance matrix and Cholesky decomposition

Treatment	**Covariance matrix**			**Cholesky Decomposition**		
D+P		*Intercept*	*Scale*		*Intercept*	*Scale*
(3-weekly)	*Intercept*	0.002981		*Intercept*	0.0546	
	Scale	0.000925	0.001918	*Scale*	0.016941	0.040391
D+ P		*Intercept*	*Scale*		*Intercept*	*Scale*

(weekly)	*Intercept*	0.001998		*Intercept*	0.0447	
	Scale	0.000413	0.001354	*Scale*	0.009239	0.035621
M+P		*Intercept*	*Scale*		*Intercept*	*Scale*
	Intercept	0.001998		*Intercept*	0.0447	
	Scale	0.000356	0.001376	*Scale*	0.007964	0.036235

Since hazards are instantaneous these need to be converted to a transition probability for a given time period (e.g. cycle) and require use of the integrated hazard function. For the Weibull distribution the integrated hazard function is:

$$H(t) = \int_0^t h(u)du = \lambda u^{\gamma} .$$

Using this formula, the hazard rate was estimated for each of the monthly cycles of the model. Following this procedure, the hazard rates were then converted into transition probabilities using standard techniques. The (mean) hazard and associated transition probabilities used in the first 12 cycles of the model are shown in Table 30 for illustrative purposes, demonstrating how the probabilities differ by intervention and by number of cycles.

Table 30: Mean hazard and associated transition probabilities

	D+P (3-weekly)		**D+P (weekly)**		**M+P**	
Cycle	**Hazard**	**Prob**	**Hazard**	**Prob**	**Hazard**	**Prob**
1	0.0070	0.0070	0.0058	0.0057	0.0074	0.0073
2	0.0134	0.0134	0.0126	0.0126	0.0153	0.0151
3	0.0178	0.0176	0.0179	0.0177	0.0210	0.0207
4	0.0214	0.0211	0.0225	0.0222	0.0258	0.0255
5	0.0245	0.0242	0.0266	0.0263	0.0302	0.0297
6	0.0273	0.0270	0.0305	0.0301	0.0341	0.0336
7	0.0299	0.0295	0.0342	0.0336	0.0379	0.0371
8	0.0323	0.0318	0.0376	0.0369	0.0414	0.0405
9	0.0346	0.0340	0.0409	0.0401	0.0447	0.0437
10	0.0368	0.0361	0.0441	0.0432	0.0478	0.0467

11	0.0388	0.0381	0.0472	0.0461	0.0509	0.0496
12	0.0408	0.0400	0.0502	0.0490	0.0538	0.0524

Since patient-level data were not available for any of the other comparators it was necessary to derive an estimate of the relative treatment effect for these to be applied in the model. Using the Bucher approach outlined in the clinical effectiveness review, indirect hazard ratios were estimated in order to include other comparators in the economic model. In order to reflect the potential correlation between the different interventions, docetaxel-based regimens were assessed via an estimate of the indirect hazard ratio versus D+P (3-weekly) and mitoxantrone/prednisone strategies were assessed via the indirect hazard ratio in relation to M+P. The indirect hazard ratios for these additional comparators are shown in Tables 31 and 32. The uncertainty associated with each hazard ratio was characterised by assigning a normal distribution to the (log) hazard. The hazard ratio was then applied to the absolute hazard for either D+P (3-weekly) or M+P and then converted in order to obtain the required transition probability.

Table 31: Indirect hazard ratios versus D+P (3-weekly)

Intervention	HR	LN (HR)	SE	Distribution
D+E	1.053	0.051	0.142	Normal
D+E+P (70)	1.237	0.213	0.338	Normal
D+E+P (35)	1.132	0.124	0.159	Normal

Table 32: Indirect hazard ratios versus M+P

Intervention	HR	LN (HR)	SE	Distribution
P	1.01	0.010	0.098	Normal
M+P+C	1.054	0.052	0.151	Normal

Quality-Adjustment (QALYs)

In order to estimate QALYs, it is necessary to quality-adjust the period of time the average patient is alive within the model using an appropriate utility or preference score. Ideally, utility data are required which quantify the potential health status of patients with mHRPC (as opposed to prostate cancer more generally) and which can be used to quantify the impact of the different treatment regimens in terms of their

impact on quality of life (QoL) i.e. adverse events and/or palliative benefits. In the absence of suitable utility values identified in the clinical and cost-effectiveness review, we conducted a separate review of other potential sources which could be used to inform this part of the economic analysis.

Methods

For the assessment of QoL a separate systematic search of relevant databases was undertaken. Full details of the search strategy are reported in Appendix 10.1.2. After removing duplicates, a total of 205 potential references were identified. Two reviewers independently screened the titles and abstracts of the studies identified from all searches and sources. A full paper copy of any study judged to be relevant by either reviewer was obtained where possible.

In total 14 abstracts were identified which were deemed to potentially provide relevant utility values for the QoL of patients with mHRPC. These 14 records were ordered as full papers. All the full articles received were subsequently screened for the presence of relevant prostate cancer QoL estimation. Studies which did not report any QoL values for metastatic disease were subsequently excluded. In total 7 studies were identified which reported potentially suitable QoL utility values.

The main QoL data reported in the studies were extracted and are reported in detail in Appendix 10.10, alongside a detailed summary of the methods and results for each study. These data are also presented in a summary results table and graphically as a spectrum of utility values for patients with prostate cancer. The summary results table is used to compare the valuation method, source of valuations and the values reported (and definitions) of the different prostate cancer health states considered. The spectrum of utility values for the health related QoL of patients with prostate cancer is used to provide a visual representation of where the different utility values reported for the health states lie on a scale representing the spectrum of prostate cancer (i.e localised, metastatic and mHRPC). Although this scale is subjective, it does help to try and contextualise the different estimates.

Results

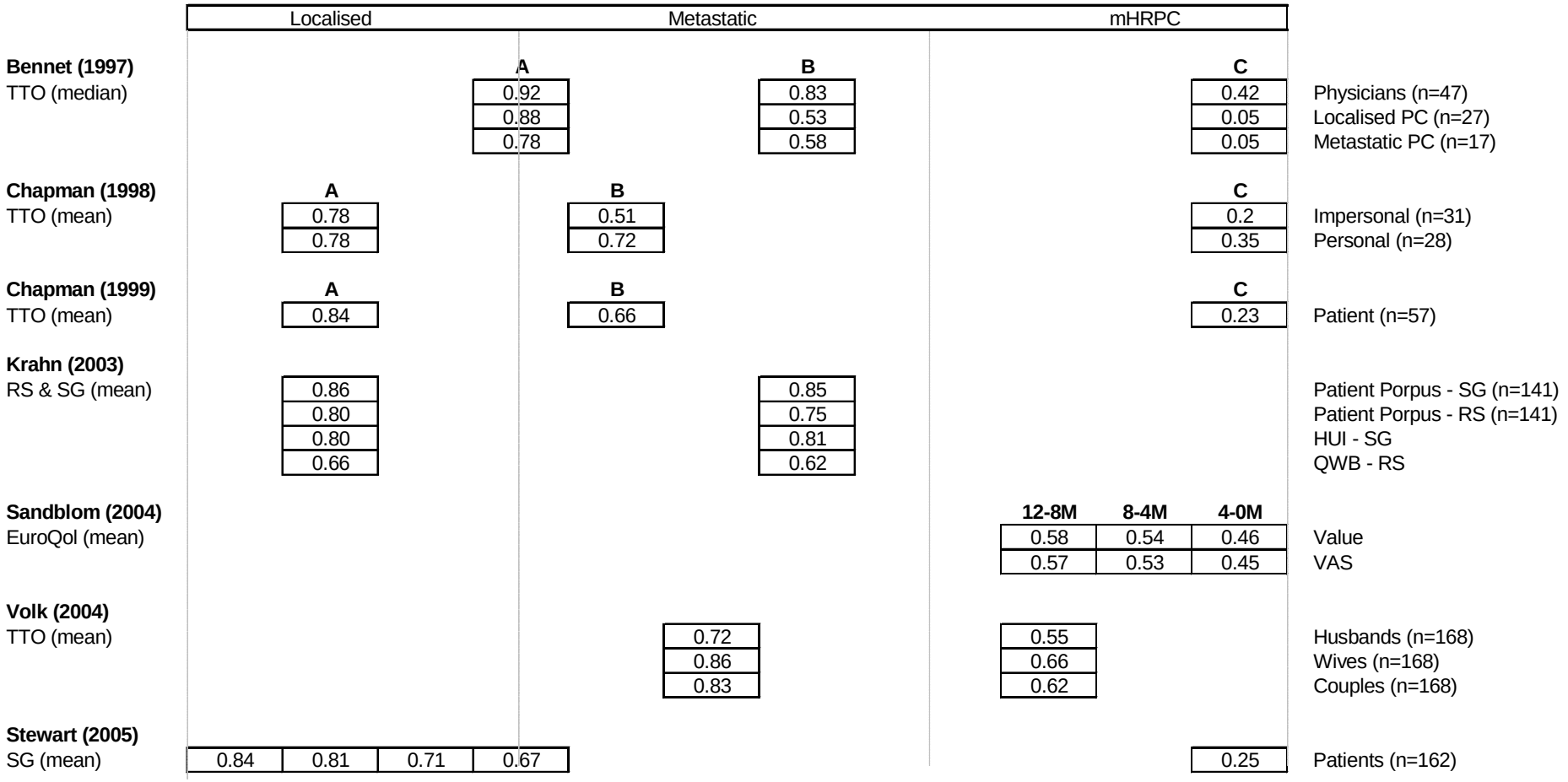
The summary results table and the spectrum of health quality of life's utility values of patients with prostate cancer, based on the 7 studies, are presented in Table 33 and Figure 5 respectively.

The range of values identified demonstrated considerable variation, ranging from 0.05 to 0.92. One of the main issues with these articles was to establish a correspondence between the different clinical health state descriptions. Effectively, each study has described the prostate cancer health states using different approaches (e.g. alternative health state descriptions, different valuation methods and different sources of values). To compound this problem, the range of values identified included values reported across the entire spectrum of prostate cancer (i.e. not just for mHRPC). Presenting these results graphically, in terms of the spectrum covering the major health states for prostate cancer, enables some of this variation to be explained by the stage of disease to which these values relate. Figure 5 illustrates that the range of values identified for metastatic disease (ranging from between 0.58 to 0.05) demonstrates less variation than the entire range of values considered across the whole disease spectrum. However, clearly the values reported for mHRPC still displayed significant variation, both in terms of the approach used to derive these values and the values themselves. As such the question of what constitutes a reliable measure of utility for this patient population needs further consideration. Each of these studies is summarised briefly below in order to assess the appropriateness of the values reported in each for the purpose of the economic model.

Table 33: Quality of life summary results table

Study	Method	Health State	Source of Values and Results
Bennet (1997)	TTO	A=Mild B=Moderate C=Severe	Physicians (Median), A = 0.92; B = 0.83; C= 0.42 Patients with localized prostate cancer (Median), A = 0.88; B = 0.53; C= 0.05 Patients with metastatic prostate cancer (Median), A = 0.78; B = 0.58; C= 0.05
Chapman (1998)	TTO	A=Mild B=Moderate C=Severe	Patients in personal version (Mean), A = 0.78; B = 0.72; C = 0.35 Patients in impersonal version (Mean), A = 0.78; B = 0.51; C = 0.20
Chapman (1999)	TTO	A=Mild B=Moderate C=Severe	Patients with localized or metastatic prostate cancer (Mean), A = 0.84; B = 0.66; C = 0.23
Krahn (2002)	PORPUS, HUI, QWB	A=Metastatic disease B=Non-metastatic disease	Patients with metastatic disease: PORPUS – SG (Mean), A = 0.85 Patients with metastatic disease: PORPUS – RS (Mean), A = 0.75 Patients with non-metastatic disease: PORPUS – SG (Mean), B = 0.86 Patients with non-metastatic disease: PORPUS – RS (Mean), B = 0.80 Community: HUI (Mean), A = 0.81; B = 0.80 Community: QWB (Mean), A = 0.62; B = 0.66
Sandblom (2004)	EQ-5D	Time of death (0-4 months) Time of death (4-8 months) Time of death (8-12 months) Average (0-12 months)	Value Score (Mean) = 0.46; VAS Score (Mean)= 0.45 Value Score (Mean) = 0.52; VAS Score (Mean)= 0.53 Value Score (Mean) = 0.58; VAS Score (Mean)= 0.57 Value Score (Mean) = 0.538; VAS Score (Mean)= 0.54
Volk (2004)	TTO	A=Hormonally responsive B=Hormone refractory	Husbands (Mean), A = 0.72; B = 0.55 Wives (Mean), A = 0.86; B = 0.66 Couples (Mean), A = 0.83; B = 0.62
Stewart (2005)	SG	A=Cancer with 20% chance of tumour spread B=Cancer with 40% chance of tumour spread C=Cancer with 70% chance of tumour spread D=Cancer with tumour spread E=Terminal disease	Patients (Mean), A = 0.84; B = 0.81; C = 0.71; D = 0.67; E = 0.25

Figure 5: Spectrum of health quality of life's utility values for prostate cancer



The study by Bennet et al (1997) assessed three separate health states in metastatic prostate cancer.[73] Valuations were provided by physicians (n= 43) and patients with both localized (n= 27) and metastatic cancer (n= 17) using a time trade-off approach. The results showed that physicians appeared more optimistic about the quality of life outcomes, associated with the different states, than the patients and hence provided higher valuations for each of the states considered.

In the first study by Chapman et al (1998), 59 patients with localized or metastatic prostate cancer evaluated three separate prostate cancer health state descriptions, including one state representing localized prostate cancer (State A) and two states based on different severity levels for metastatic prostate cancer (B = moderate, C= severe).[74] TTO valuations were obtained from either a personal (n=28) or impersonal (n=31) description of the health states. The results are difficult to interpret since several changes were applied to the health state descriptions used during the course of the study.

In the second study reported by Chapman et al (1999), 57 patients with localized or metastatic prostate cancer evaluated three separate prostate cancer health state descriptions, including one state representing localized prostate cancer (State A) and two states based on different severity levels for metastatic prostate cancer (B = moderate, C= severe).[75] TTO valuations were obtained from either a personal or impersonal description of the health states. These were combined when the final results were presented, and hence it is difficult to assess the potential impact of the different descriptions on the overall valuations provided.

In the study by Krahn et al (2003), 141 prostate cancer patients assessed two main health states representing different stages of prostate cancer: non-metastatic and metastatic disease.[76] Differences between the community and patients preferences were assessed using patient valuations (from rating scales and standard gamble approaches) and community valuations (from HUI and QWB). The results demonstrated that patients appeared to value their current health state (either metastatic or non-metastatic disease) higher than the community. In addition the

utility values derived from standard gamble approaches were higher than those obtained from rating scales.

The study by Sandblom et al (2004), assessed the quality of life in patients with prostate cancer (1237 patients) using a multi-attribute utility instrument (EuroQol – EQ-5D).[77] Sandblom reported that the quality of life of the population of men with prostate cancer decreases during the final year of life, with a range of (mean) utility values from 0.58 to 0.46 covering different periods during the last 12-months of a patient's life. The average value reported across the final year was reported to be 0.538 (95% CI = +/- 0.077). Severe pain was reported the last week before death, and afflicted 25.8% of the patients who died of prostate cancer.

The study by Volk et al (2004) reported utility values based on responses from participants attending a prostate screening programme.[78] Values were obtained separately from the male subjects and their wives and also during a joint interview in which the preferences of the couples were also elicited. The health states depicted comprised both hormone dependent metastatic prostate cancer and hormone-refractory metastatic prostate cancer. The results demonstrated differences in the valuations reported for the two health states based on the different sources of valuations (i.e. husband, wife and couple). The results showed that most husbands appeared willing to trade some longevity in life to avoid the metastatic prostate cancer scenarios. As a result, the valuations reported by the male participants were lower than both those provided by their wives and those provided jointly by the couple.

In the final study by Stewart et al (2005), 162 men (including 52% with prostate cancer) evaluated five main prostate cancer health states.[79] These health states comprised four "asymptomatic" states each with a different probability of tumour spread (20%, 40%, 70% and 100%) and a terminal "symptomatic" health state. For each health state, valuations were elicited using a Standard Gamble (SG) approach. The results demonstrated a lower utility value associated with an increasing probability of tumour spread (0.84 to 0.67). For the final terminal health state, the utility value was estimated to be 0.25.

Conclusion

All the articles included for the determination of prostate cancer patients' QOL provided potentially useful summary values and an interesting overview of the impact of prostate cancer from different perspectives (e.g. patient, physician, partner). Across the full range of values identified there was considerable variation in the utility values reported. Some of this variation was simply due to the spectrum of health states reported in each of the studies, often covering localised as well as metastatic disease (e.g. the studies by Chapman et al (1998 & 1998) reported utility scores for three health outcomes corresponding to the beginning and end of the hormone dependent metastatic prostate cancer, and also for the end of the mHRPC state). However, within the studies identified that reported values specifically for metastatic disease there was less variation. Of the variation that remained, some of this can be attributed to the different valuation methods used (e.g. TTO vs. multi-attribute utility instruments), the different health state descriptions (e.g. early vs. late mHRPC) and the different sources for the health state values (e.g. patient, physician, societal etc).

The only study reporting societal valuations using a standardised and validated generic instrument (and hence meeting the Reference Case requirements outlined in the recent NICE guidance), and representative of the population under consideration here, was the study by Sandblom et al.[77] This study provides a robust quality of life valuation based on the year before death for prostate cancer patients. The average value (and 95% CI) reported for all patients who died at any stage during the 12-months following completion of the questionnaire was used as the main probabilistic input into the economic model. No suitable estimates were identified which would enable the impact of the different side-effects considered in the clinical-effectiveness review to be considered.

Resource use and costs

Resource utilisation and cost data were based on the drug acquisition and administration costs for each intervention and subsequent follow-up costs including the management of side-effects, further chemotherapies and palliative care. The follow-up costs were based on the patient-level cost data reported in the submission by Sanofi-Aventis. In order to estimate the costs of prednisone/prednisolone alone,

additional patient-level data from the cost-effectiveness study by Bloomfield et al[64] was obtained.

The drug acquisition costs for each intervention were calculated according to the protocol dosages reported in the trials. Unit costs are reported in Table 34. These are based on undiscounted prices from the British National Formulary (BNF).[80] Dosages were multiplied by a body surface area of 1.9m^2. The costs of pre-medication (oral dexamethasone) were included for docetaxel regimens and a daily dose of 2 mg warfarin was applied to interventions using estramustine.

Table 34: Unit costs of drugs

Drug	Unit Cost	Source
Docetaxel – 2 ml vial	£534.75	BNF
Docetaxel – 0.5 ml vial	£162.75	BNF
Prednisolone – 28 * 5 mg tablets	£0.68	BNF
Dexamethasone 4mg/ml – 2 ml injection	£1.98	BNF
Dexamethasone 24mg/ml – 5 ml injection	£16.66	BNF
Mitoxantrone – 12.5 ml vial (Okantrone)	£169.25	BNF
Estramustine – 100 * 140 mg tablets	£171.28	BNF
Warfarin – 28 * 1 mg tablet	£1.39	BNF
Clodronate – 5ml (Bonefos)	£11.02	BNF

The total drug costs were applied to the mean number of cycles of chemotherapy. The mean number of cycles for D+P (3-weekly) and M+P was reported in the submission by Sanofi-Aventis. Additional information was also provided on request for the mean number of cycles for D+P (weekly). In order to quantify uncertainty in these estimates, additional information was also provided to enable the standard error to be estimated for all 3 comparators. In the absence of comparable estimates for the mean number of cycles from the other trials considered in the clinical-effectiveness review, we used the same

estimates reported for D+P (3-weekly) and M+P for the remaining docetaxel and mitoxantrone-based regimens. Full details of the costs of each intervention are reported in Appendix 10.11. The total costs are summarised in Table 35.

Chemotherapy was assumed to be administered on an outpatient basis for all chemotherapy-based regimens and a unit cost of £177 was applied for each attendance based on the cost of an oncology outpatient attendance.[81]

Table 35: Total drug costs for each intervention

Intervention	Mean no. of cycles (SE)	Total Drug cost
D+P (3-weekly)	7.3 (0.18)	£7,858
D+P (weekly)	3.7 (0.08)	£18,970
D+E	7.3 (0.18)	£7,035
D+E+P(70)	7.3 (0.18)	£8,531
D+E+P(35)	7.3 (0.18)	£9,235
M+P	5.9 (0.17)	£1,005
M+P+C	5.9 (0.17)	£1,330
P	NA	£1.48 per month

Follow-up costs were derived from the data reported in the submission by Sanofi-Aventis. These costs comprised the costs of managing side-effects, subsequent chemotherapies and hospitalisations for palliative care. The costs for these different components for D+P (3-weekly) and M+P were reported separately in the submission, with the costs of subsequent chemotherapy and hospitalisations accounting for between 70-80% of these costs. However, as noted in the economic review, it was unclear how censoring had been accounted for in these estimates. In order to ensure that censoring was appropriately considered, we used the costs reported in the submission based on the Lin method[69] for handling censored cost data. Details of the mean follow-up costs for 8 intervals (0-6 months and 4 monthly intervals thereafter) were reported by Sanofi-Aventis and were used as the basis for the follow-up cost inputs applied in our model.

In order to reflect the additional terminal care costs incurred by patients in the last month of life we assigned a one-off cost to the transition to the dead state. In the absence of data on these additional costs we estimated them from those patients who died within the first 6 months, as reported by Sanofi-Aventis. This terminal care component was then subtracted from the total follow-up costs associated with each of the other periods. In the absence of specific patient level information detailing costs per monthly cycle, all follow-up costs were assigned as patients died (cycle). For the purposes of discounting, terminal care costs were discounted at the rate for the appropriate cycle and other follow-up costs were discounted based on the mid-point of the follow-up period reported.

Additional information was requested to quantify the sample uncertainty in these estimates, however this information could not be provided. In the absence of these data, we made the assumption that the standard error was equal to one half of the mean value (i.e. the coefficient of variation was 0.5) as suggested by Briggs et al.[70] A gamma distribution was assigned to each follow-up period using the methods of moments approach.[70]

In the absence of specific patient level information detailing costs for each of the treatments considered in analysis 2 we made the following assumptions. The follow-up costs for docetaxel plus prednisone/prednisolone 3-weekly (D+P (3-weekly)) were used as the basis for the follow-up costs for all regimens incorporating docetaxel. Hence, the only differences assumed in the costs modelled for these treatments were those due to differences in acquisition costs and in overall survival. A similar approach was used to model the costs of M+P+C based upon the follow-up costs reported for mitoxantrone and prednisone. Tables 36 and 37 report the follow-up costs applied to the models and the parameters of the associated gamma distributions.

Table 36: Follow-up costs for docetaxel regimens

Docetaxel regimens	Mean	SE	Distribution	alpha	beta
Terminal care cost	£3,527.95	£1,763.98	Gamma	4.00	881.99
6-10 months	£1,551.29	£775.65	Gamma	4.00	387.82

10-14 months	£718.40	£359.20	Gamma	4.00	179.60
14-18 months	£1,461.49	£730.75	Gamma	4.00	365.37
18-22 months	£7,616.34	£3,808.17	Gamma	4.00	1,904.09
22-26 months	£6,674.97	£3,337.49	Gamma	4.00	1,668.74
>26 months	£4,827.96	£2,413.98	Gamma	4.00	1,206.99

Table 37: Follow-up costs for mitoxantrone regimens

Mitoxantrone Regimens	**Mean**	**SE**	**Distribution**	**alpha**	**beta**
Terminal care cost	£3,942.16	£1,971.08	Gamma	4.00	985.54
6-10 months	£3,080.91	£1,540.46	Gamma	4.00	770.23
10-14 months	£1,753.84	£876.92	Gamma	4.00	438.46
14-18 months	£4,779.66	£2,389.83	Gamma	4.00	1,194.92
18-22 months	£3,286.83	£1,643.42	Gamma	4.00	821.71
22-26 months	£8,079.19	£4,039.60	Gamma	4.00	2,019.80
>26 months	£12,679.52	£6,339.76	Gamma	4.00	3,169.88

No data were provided within the company submission regarding the potential follow-up costs associated with non-chemotherapy regimens (i.e. prednisone/prednisolone alone). However, as detailed previously in the review of published cost-effectiveness analyses, Bloomfield et al[64]reported the results of the costs and outcomes for a comparison of M+P versus P. This study was used to estimate the costs of P on the basis of an adjustment to the costs of M+P. We requested additional patient level data from one of the authors of the Bloomfield study (personal correspondence A Willan). On the basis of the data provided an adjustment was made based on the relative differences in the follow-up costs between M+P and P. Costs were converted from Canadian dollars to pounds sterling using the appropriate exchange rate based on the price year used in the Bloomfield study. Gamma distributions were assigned to the total follow-up cost for each treatment using the patient level data, thus enabling the uncertainty in the relative difference to be characterised. The mean estimate for this relative difference was calculated to be 1.26 (i.e. follow-up costs were assumed, on average, to be 26% higher for patients receiving P as part of their initial treatment in

comparison to patients receiving M+P) . This estimate was applied to the total follow-up cost estimated for M+P.

6.4. Analytic methods

The overall model is run for a period of 180 cycles (equivalent to 15 years), after which the vast majority of patients will have died in the model. Therefore, the mean LYG and QALYs per patient can be calculated for each strategy, as well as the mean lifetime costs.

The model has been developed in Excel. The Monte-Carlo simulation was run for 5,000 iterations. The model is run several times, once for the main analysis and then for a number of alternative sensitivity analyses to consider alternative assumptions related to the discount rate and quality of life estimates.

The results are presented in two ways. Firstly, mean costs and QALYs for the various comparators are presented and their cost-effectiveness compared using standard decision rules and estimating ICERs as appropriate.[82] The ICER examines the additional costs that one strategy incurs over another and compares this with the additional benefits. When more than two interventions are being compared the ICERs are calculated using the following process:

i) The strategies are ranked in terms of cost (from the least expensive to the most costly).
ii) If a strategy is more expensive and less effective than any previous strategy, then this strategy is said to be dominated and is excluded from the calculation of the ICERs.
iii) The ICERs are calculated for each successive alternative, from the cheapest to the most costly. If the ICER for a given strategy is higher than that of any more effective strategy, then this strategy is ruled out on the basis of extended dominance.

Finally, the ICERs are recalculated excluding any strategies that are ruled out by principles of dominance or extended dominance.

Given that mean costs and QALYs gained are estimated with uncertainty, the output from the simulations were then used to generate cost-effectiveness acceptability curves (CEACs) for the alternative analyses. These curves detail the probability that each intervention is cost-effective over a range of potential maximum values that the health service is prepared to pay for an additional QALY.[83]

6.5. Results

The results are presented separately for a comparison of D+P (3-weekly), M+P and P (Analysis 1) and for the full range of potential comparators (Analysis 2).

Results for Analysis 1

Table 38 presents the lifetime analysis of the ICER for the comparison of docetaxel plus prednisone/prednisolone (D+P (3-weekly)), mitoxantrone plus prednisone/prednisolone (M+P) and prednisone/prednisolone (P). Mean LYG are presented for comparative purposes only, in order to allow comparison with the results reported in the submission by Sanofi-Aventis. In this analysis, P is dominated by M+P (i.e. P is more expensive and marginally less effective). The calculation of the ICER is thus based on a comparison between D+P (3-weekly) and M+P. The ICER of D+P (3-weekly) compared to M+P is £32,706 per additional QALY. Hence the results of Analysis 1 indicate that D+P (3-weekly) is cost-effective provided that the NHS is prepared to pay at least this amount per additional QALY. For lower cost-per-QALY thresholds, M+P is cost-effective.

Table 38: Analysis 1 - Estimates of mean lifetime costs and QALYs for D+P (3-weekly), M+P and P, together with incremental analysis

Intervention	Cost	LYG	QALY	ICER	Probability cost-effective		
					@£20k	@£30k	@£40k
P	£11,227	1.50	0.81001	Dom	39%	33%	26%
M+P	£10,834	1.51	0.81364	-	39%	29%	20%
D+P (3-weekly)	£15,883	1.80	0.96801	£32,706	22%	38%	53%

Figure 6 presents the decision uncertainty in the form of mutiple CEACs. The CEACs demonstrate that the probability that D+P (3-weekly) is cost-effective increases as the maximum willingness to pay increases: if society is prepared to pay £20,000 for an additional QALY, the probability that D+P(3-weekly) is cost effective is only around 22%, increasing to 53% if the maximum willingness to pay is £40,000.

Figure 6: Cost-effectiveness acceptability curves for the decision between D+P (3-weekly), M+P and P

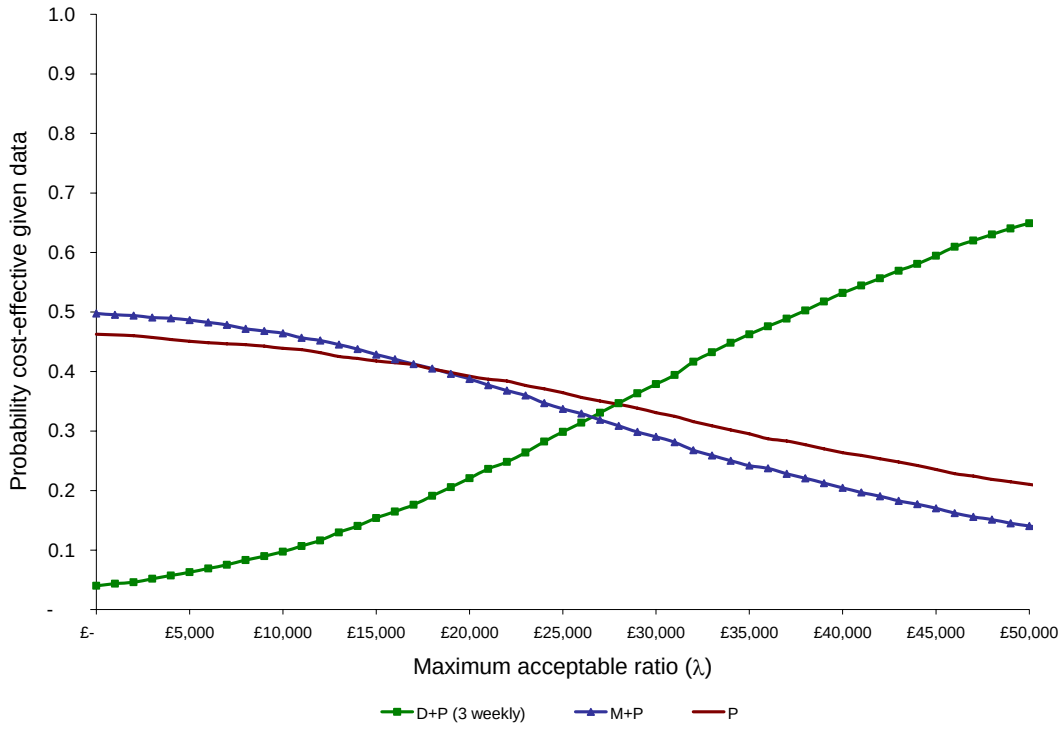
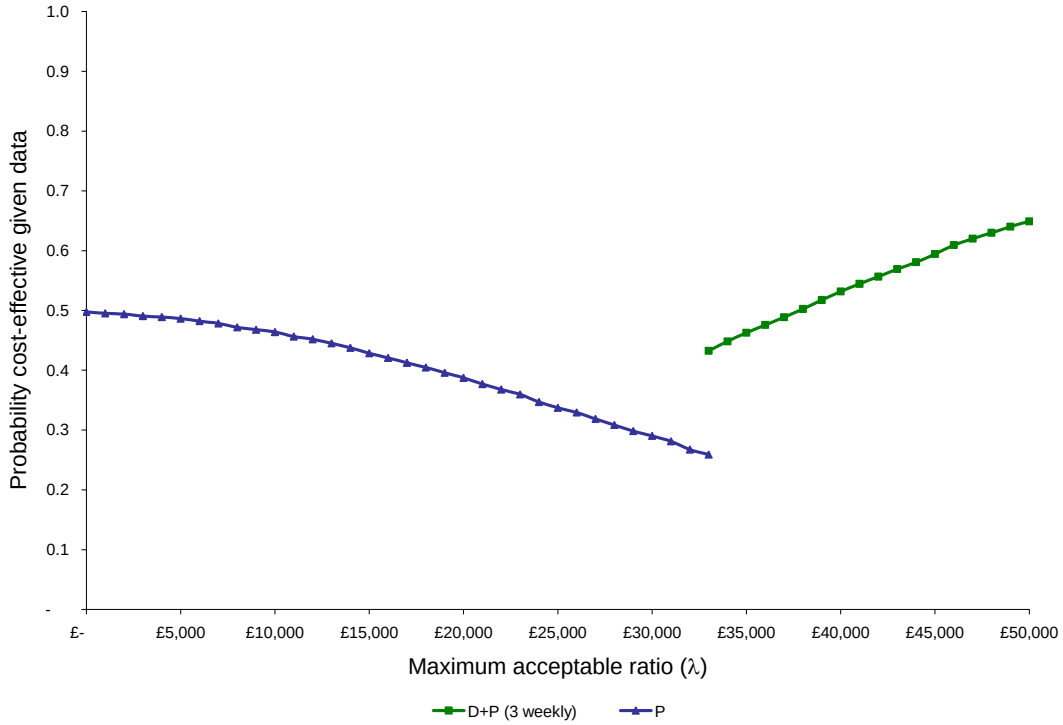


Figure 7: Cost-effectiveness acceptability frontier for the decision between D+P (3-weekly), M+P and P



Although the CEAC provides a useful graphical representation of the uncertainty associated with the probability that individual strategies are cost-effective over a range of threshold values, the results of the CEAC can only be used to identify the optimal implementation decision under a restrictive set of assumptions. This is because the strategy with the highest probability of being cost-effective does not necessarily have the highest expected pay-off (i.e. net benefit), and will only do so when the distribution of these pay-offs are symmetrical.[83] This limitation can be overcome by using a cost-effectiveness frontier to indicate which strategy is optimal (and the associated probability that this strategy is the most cost-effective) across the range of values representing the maximum amount the NHS is prepared to pay for an additional QALY.[83] The frontier for this analysis is provided in Figure 7, demonstrating which intervention is cost-effective (and the probability this intervention is the most cost-effective) across the range of cost-per-QALY thresholds considered.

Results for Analysis 2

Table 39 presents the lifetime analysis of the ICER for the comparison of the full range of comparators identified as part of the clinical effectiveness review. In this analysis a total of 8 strategies were considered, including a range of alternative chemotherapy regimens in which docetaxel was used. In this analysis, P and M+P+C are dominated by M+P. In addition, D+P (3-weekly) dominates D+P (weekly) and D+E+P (35 and 70). Although D+E is not dominated by any strategy, it is ruled out of the ICER calculations on the grounds on extended dominance by D+P (3-weekly). Hence, although Analysis 2 includes a broader range of comparators, the final ICER calculations are based on the same non-dominated interventions as in Analysis 1. Consequently, the ICER of D+P (3-weekly) compared to M+P is identical to that presented previously i.e. £32,706 per additional QALY. As a result the same conclusions can be drawn regarding the optimal intervention based on cost-effectiveness considerations.

Table 39: Analysis 2 - Estimates of mean lifetime costs and QALYs for the full range of potential comparators, together with incremental analysis

Intervention	Cost	LYG	QALY	ICER	Probability cost-effective		
					@£20k	@£30k	@£40k
M+P+C	£11,008	1.47	0.79299	Dom	25%	17%	12%
P	£11,227	1.50	0.81001	Dom	28%	22%	16%
M+P	£10,834	1.51	0.81364	-	18%	12%	7%
D+P (weekly)	£26,268	1.57	0.84636	Dom	0%	0%	0%
D+E+P (70)	£16,260	1.60	0.86334	Dom	8%	12%	16%
D+E+P (35)	£18,460	1.68	0.90168	Dom	1%	2%	4%
D+E	£15,036	1.75	0.94209	Ext Dom	13%	21%	25%
D+P (3-weekly)	£15,883	1.80	0.96801	£32,706	7%	14%	20%

Although the ICER calculations are the same in both Analyses 1 and 2. The addition of more comparators results in increased decision uncertainty. Figure 8 presents the CEACs for Analysis 2. The CEACs demonstrate that while the probability that D+P (3-weekly) is cost-effective increases as the maximum willingness to pay increases, the absolute probabilities are now reduced compared to Analysis 1. If society is prepared to pay £20,000 for an additional QALY, the probability that D+P(3-weekly) is cost effective is now only around 7% (compared to 22% in Analysis 1), increasing

to 20% (compared to 53%) if the maximum willingness to pay is £40,000. The increased decision uncertainty surrounding the optimal intervention, across the range of threshold values for the cost per additional QALY considered, in highlighted by the cost-effectiveness frontier in Figure 9.

Figure 8: Cost-effectiveness acceptability curves for the decision between D+P (3-weekly), M+P, P, D+P (weekly), D+E, D+E+P (70), D+E+P (35) and M+P+C

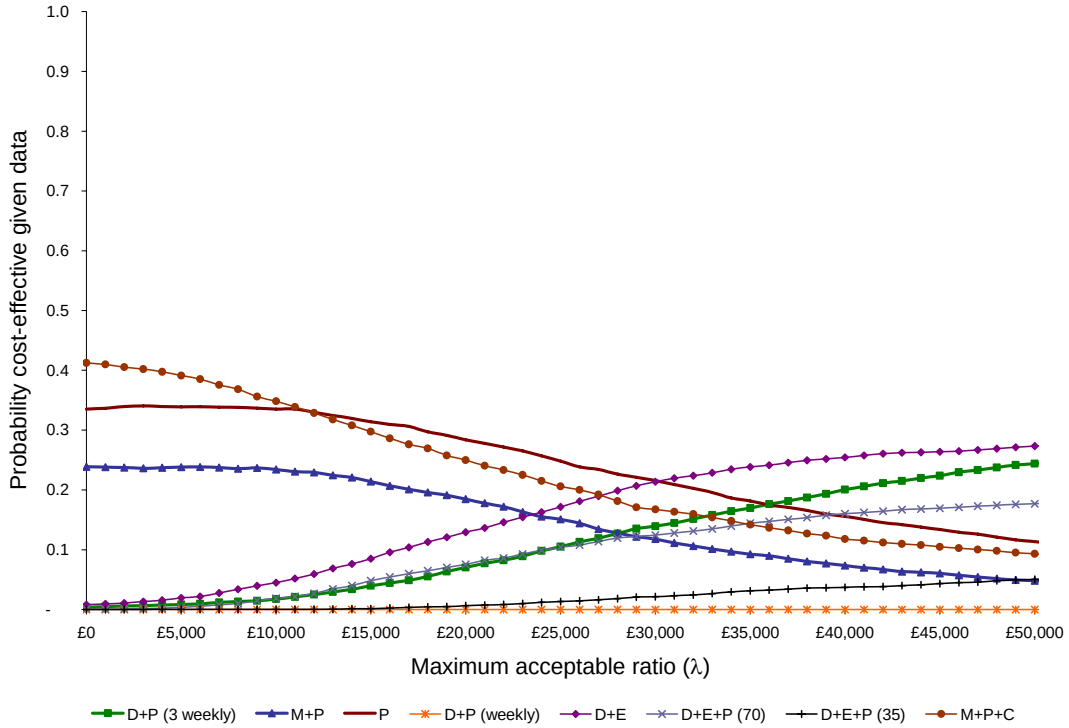
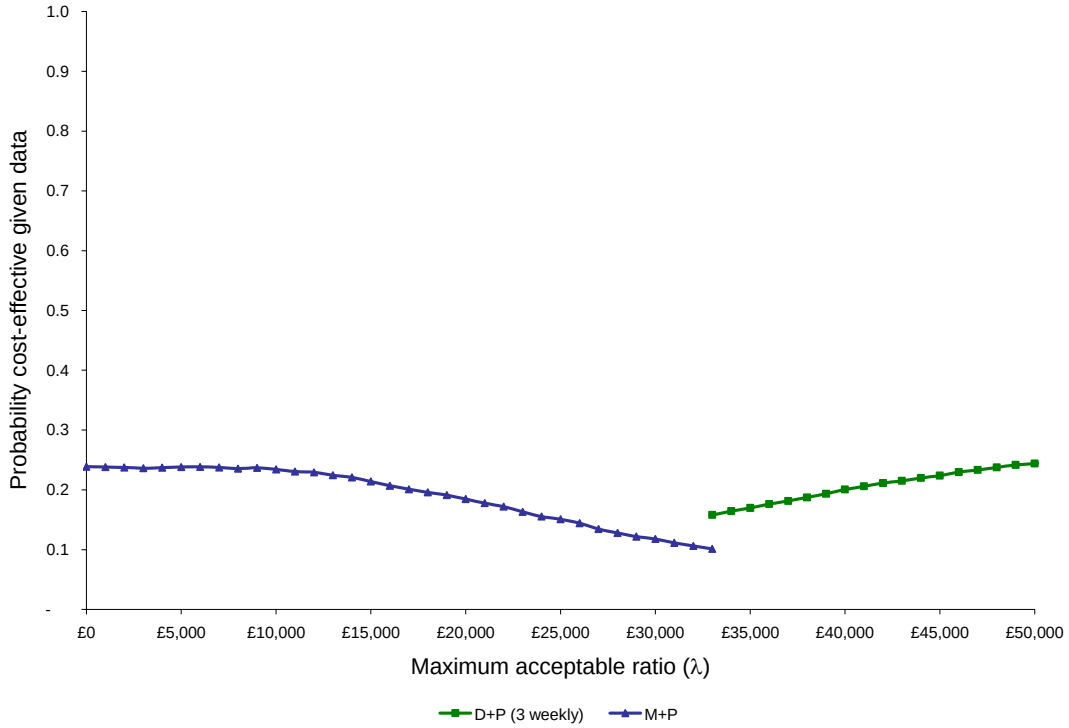


Figure 9: Cost-effectiveness acceptability frontier for the decision between D+P (3-weekly), M+P, P, D+P (weekly), D+E, D+E+P (70), D+E+P (35) and M+P+C



6.6. Sensitivity analysis

A series of sensitivity analyses were undertaken to explore the robustness of the main results to alternative assumptions related to the discount rate applied to costs and outcomes and the approach used to estimate QALYs in the main analysis.

The first of these analyses applied a discount rate of 6% for costs and 1.5% for outcomes. Tables 40 and 41 report the results for this particular sensitivity analysis. The use of differential discount rates for costs and benefits did not lead to a marked difference compared to the results reported in the main analysis. In Analysis 1, the ICER for D+P (3-weekly) was £31,674 per QALY, in comparison with M+P. In Analysis 2, D+E was no longer ruled out on the grounds of extended dominance. Hence, the ICER for D+P (3-weekly) was £31,890 per QALY, in comparison with D+E.

Table 40: Analysis 1 - Estimates of mean lifetime costs and QALYs for D+P (3-weekly), M+P and P using alternative discount rates

Intervention	Cost	LYG	QALY	ICER	Probability cost-effective		
					@£20k	@£30k	@£40k
P	£10,775	1.53	0.82172	Dom	39%	32%	26%
M+P	£10,441	1.54	0.82531	-	39%	28%	19%
D+P (3-weekly)	£15,554	1.84	0.98674	£31,674	23%	40%	55%

Table 41: Analysis 2 - Estimates of mean lifetime costs and QALYs for the full range of potential comparators using alternative discount rates

Intervention	Cost	LYG	QALY	ICER	Probability cost-effective		
					@£20k	@£30k	@£40k
M+P+C	£10,595	1.49	0.80060	Dom	23%	16%	11%
P	£10,775	1.53	0.82172	Dom	27%	20%	14%
M+P	£10,441	1.54	0.82531	-	19%	12%	7%
D+P (weekly)	£25,983	1.60	0.85705	Dom	0%	0%	0%
D+E+P (70)	£15,989	1.65	0.88468	Dom	8%	14%	17%
D+E+P (35)	£18,176	1.71	0.91887	Dom	1%	2%	4%
D+E	£14,629	1.78	0.95772	£31,627	14%	22%	26%
D+P (3-weekly)	£15,554	1.84	0.98674	£31,890	8%	14%	20%

One potential limitation of the current analysis is that the final QALY calculations do not incorporate any assessment of the potential impact of adverse events on quality of life. Given that both the probability and types of adverse events are likely to differ between the interventions considered, it is important that this issue is given due consideration. In addition, as part of our review of utility estimates for HRPC patients, we only identified a single study reporting societal valuations using a standardised and validated generic instrument for the main utility estimates.[77] Although this study was considered the most appropriate source of utility for the purposes of our main analysis, the review demonstrated considerable variation within the other estimates identified. While some of this variation can be attributed to the different methods of valuing particular health states (e.g. expert, patient, societal perspective etc), the degree of variation also suggests that the particular health state descriptive system applied could also lead to different utility estimates.

Two additional sensitivity analyses have therefore been undertaken to explore the robustness of the main analysis to alternative assumptions related to these aspects of quality of life. The first of these analyses addresses the issue of adverse events through a series of adjustments to the utility values applied in the main analyses. In order to attempt to characterise the differential impacts for each intervention, separate adjustments were made for each of the main types of chemotherapy (docetaxel, mitoxantrone and estramustine). The second analysis separately considers the impact of variation in the utility data using values derived from an alternative health state descriptive system. Due to the lack of suitable data identified as part of our review for these analyses, it was necessary to undertake a separate valuation exercise in order to generate societal valuations for these sensitivity analyses.

In conjuction with the NHS Value in Health Panel project additional scenarios were developed in order to explore these areas in more detail. The Value of Health Panel is a collaborative methodological project being carried out by the Universities of Exeter, Southampton and Sheffield. A group of members of the public (n=92) have been recruited from the electoral registers in Exeter, Sheffield, Glasgow and Aberdeen and familiarised with the standard gamble (SG) technique for preference elicitation. Using a web based interface for SG (www.valueofhealth.org), preferences are elicited on descriptions of health states, as specified by the needs of researchers carrying out cost utility analyses. Unless pre-existing examples are used, health state descriptions are derived from disease specific quality of life measures.

The prostate cancer scenarios were developed from the FACT-P. This widely used and validated measure has good internal consistency and discriminatory ability.[84] Health state descriptions were developed from the FACT-P as follows. Firstly, the most important items on the scale were identified by a clinical expert in the management of advanced prostate cancer. These items were included in the health state description with severity being represented using, as far as possible, the categorical statements used in the FACT-P (“not at all”, “a little bit”, “somewhat”, “quite a bit”, and “very much”). Three levels of severity were represented, using the dimension specific scores by stage reported in Esper et al as a guide: early advanced disease, moderate advanced disease and late advanced disease.

Preferences were also elicited from the Value of Health Panel on the scenarios developed by Chapman et al.[75] The potential impact of adverse events of therapy was represented by the addition of statements relating to adverse events most commonly seen on each agent to the Chapman B (moderate severity) scenario.

The draft scenarios were reviewed by an oncologist and urologist with extensive experience in the management of prostate cancer and revised as necessary. The final scenarios used are reported in Appendices 10.13 and 10.14.

Adverse Event Adjustment

An adjustment was made for the potential impact of adverse events by estimating the probability of experiencing a major adverse-event (Grade III/IV) and applying a utility decrement to reflect the resulting impairment in QoL. The decrement in QALYs attributed to adverse events was then subtracted from the total QALY estimates reported in the main analyses.

The probability of Grade III/IV adverse events were estimated using a meta-analysis of Grade III/IV adverse event data using a hierarchical Bayesian model.[85] The analysis was conducted using Markov Chain Monte Carlo (MCMC) implemented in WinBUGS.[86] Details of the data and model are reported in Appendix 10.12. Summary probabilities for the different interventions are reported in Table 42. To maintain correlation between the results for each intervention, the simulated output from WinBUGS was exported directly into the main Excel model. In the absence of Grade III/IV adverse event data reported for M+P+C, we assumed that these would be the same as those reported for M+P.

Table 42: Mean (SE) estimates of the probability of a Grade III/IV adverse event from Bayesian meta-analysis

Intervention	Mean	SD
D+P (3-weekly)	0.4973	0.088
D+P (weekly)	0.4694	0.0875

D+E	0.5893	0.0852
D+E+P(70)	0.376	0.1101
D+E+P(35)	0.0455	0.0290
M+P	0.3914	0.0785
M+P+C	Same as M+P	Same as M+P
P	0.2653	0.092

Table 43 summarises the utility values based on the 27 responses from the NHS Value in Health Panel. These utility values were based on a description of a moderate disease state with and without a description of the most common adverse-events associated with the various chemotherapies.

Table 43: Utility Values including/excluding adverse-events

Health State	N	Mean	SE
Moderate Disease	27	0.7319	0.0438
Moderate Disease + Docetaxel AE	27	0.5972	0.0519
Moderate Disease + Mitoxantrone AE	27	0.6643	0.0455
Moderate Disease + Estramustine AE	27	0.6222	0.0482

These utility values were used to estimate the mean (and SE) for the utility decrement associated with the different chemotherapies (reported in Table 44). These adjustments were applied to a single cycle of the model and hence we assumed that the duration of the adverse-event (and hence the decrement) lasted for a maximum of one month. Gamma distributions were assigned to these data for the purposes of the probabilistic analysis, using method-of-moments.

Table 44: Utility decrements applied in the sensitivity analysis

Intervention	Mean	SE	Distribution
Docetaxel	0.1347	0.0679	Gamma
Mitoxantrone	0.0676	0.0632	Gamma
Estramustine	0.1097	0.0651	Gamma

In the absence of utility decrements for the complete range of possible strategies, the following assumptions were applied. The decrement reported for docetaxel was applied to the two D+P strategies (3-weekly and weekly). For the docetaxel and estramustine strategies (D+E and D+E+P 35 and 70), the decrement applied was taken as the maximum estimated for docetaxel and estramustine. The decrement reported for mitoxantrone was applied to both of the mitoxantrone-based comparators (M+P and M+P+C). Finally, in the absence of data for the adverse-event profile reported for prednisone/prednisolone, the lowest decrement across the 3 different interventions was applied. Although this approach resulted in similar decrements applied to more than one strategy, the total impact on the QALY calculations was specific for each intervention, since the probability of experiencing Grade III/IV adverse events was separately estimated for each intervention in the Bayesian meta-analysis.

Tables 45 and 46 report the results of the sensitivity analysis including the adverse events. The results demonstrate that the ICER appears robust to the inclusion of adverse events. The ICER of D+P (3-weekly) in comparison to M+P increases marginally to £33,298 per QALY when adverse events are included (compared to £32,706 per QALY in the main analyses).

Table 45: Analysis 1 - Estimates of mean lifetime costs and QALYs for D+P (3-weekly), M+P and P, including adjustment for adverse events

Intervention	Cost	LYG	QALY	ICER	Probability cost-effective		
					@£20k	@£30k	@£40k
P	£11,242	1.51	0.80103	Dom	41%	35%	28%
M+P	£10,801	1.51	0.79917	-	38%	29%	20%
D+P (3-weekly)	£15,859	1.80	0.95107	£33,298	21%	36%	51%

Table 46: Analysis 2 - Estimates of mean lifetime costs and QALYs for the full range of potential comparators, including adjustment for adverse events

Intervention	Cost	LYG	QALY	ICER	Probability cost-effective		
					@£20k	@£30k	@£40k
M+P+C	£10,962	1.47	0.77734	Dom	25%	16%	12%
P	£11,242	1.51	0.80103	Dom	29%	22%	17%
M+P	£10,801	1.51	0.79917	-	19%	13%	8%

D+P (weekly)	£26,263	1.57	0.83042	Dom	0%	0%	0%
D+E+P (70)	£16,302	1.61	0.85455	Dom	7%	12%	16%
D+E+P (35)	£18,437	1.67	0.90008	Dom	1%	3%	4%
D+E	£14,967	1.74	0.92071	Ext Dom	12%	20%	24%
D+P (3-weekly)	£15,859	1.80	0.95107	£33,298	7%	14%	20%

Variation in the health state descriptive system

Three separate health states were used to describe the progression of advanced disease in HRPC in order to reflect the QoL of early, moderate and late disease. These health state descriptions were devised using data reported using FACT-P. For the purposes of the cost-effectiveness analysis, these estimates were combined to reflect a single utility value. The utility values for each state (including the combined estimate) are reported in Table 47. The valuations provided for each of the states, and the combined estimate, were higher than the utility estimate applied in the main analysis (0.538).

Table 47: Alternative health state utility values based on scenarios developed using FACT-P

Advanced Disease State	Mean	SE
FACT-P (Early)	0.725	0.0393
FACT-P (Moderate)	0.6159	0.0501
FACT-P (Late)	0.5774	0.0476
Combined estimate	0.638	0.0462

Tables 48 and 49 report the results for Analysis 1 and 2 using the combined utility values derived from an alternative classification system based on FACT-P. The application of a higher utility estimate resulted in a more favourable ICER for docetaxel. The ICER of D+P (3-weekly) in Analysis 1 was £28,019 per QALY, compared with M+P. In Analysis 2, D+E was no longer ruled out by extended dominance. Hence the ICER of D+P (3-weekly) in Analysis 2 was calculated in comparison with D+E. The ICER for this comparison was £29,436 per QALY.

Table 48: Analysis 1 - Estimates of mean lifetime costs and QALYs for D+P (3-weekly), M+P and P, together with incremental analysis

Intervention	Cost	LYG	QALY	ICER	Probability cost-effective		
					@£20k	@£30k	@£40k
P	£11,169	1.50	0.95985	Dom	37%	29%	22%
M+P	£10,793	1.51	0.96437	-	36%	25%	16%
D+P (3-weekly)	£15,908	1.80	1.14693	£28,019	27%	47%	62%

Table 49: Analysis 2 - Estimates of mean lifetime costs and QALYs for the full range of potential comparators, together with incremental analysis

Intervention	Cost	LYG	QALY	ICER	Probability cost-effective		
					@£20k	@£30k	@£40k
M+P+C	£11,012	1.47	0.93821	Dom	21%	13%	9%
P	£11,169	1.50	0.95985	Dom	25%	17%	12%
M+P	£10,793	1.51	0.96437	-	17%	10%	6%
D+P (weekly)	£26,281	1.57	1.00274	Dom	0%	0%	0%
D+E+P (70)	£16,328	1.62	1.03320	Dom	10%	16%	18%
D+E+P (35)	£18,400	1.67	1.06452	Dom	1%	3%	4%
D+E	£15,034	1.75	1.11722	£27,744	17%	25%	28%
D+P (3-weekly)	£15,908	1.80	1.14693	£29,436	9%	18%	23%

6.7. Value of information

A non-parametric approach was used to determine the costs of uncertainty associated with the adoption decision.[87] The use of Monte Carlo simulation allows the error probability associated with the adoption decision to be expressed as the proportion of iterations which result in an adoption decision other than that selected on the basis of expected cost-effectiveness. The benefit forgone is simply the difference in the costs and outcomes (net benefit) between the optimal strategy for a given iteration and those of the strategy identified as optimal on the basis of expected cost-effectiveness estimates. The expectation of benefits forgone over all iterations represents the EVPI per individual.

Clearly since information can be of value to more than one individual, EVPI can also be expressed for the total population who stand to benefit over the expected lifetime of the programme/technology.[88, 89] If the EVPI for the population of current and future

patients exceeds the expected costs of additional research, then it is potentially cost-effective to conduct further research. The overall value of information for a population is determined by applying the individual EVPI estimate to the number of people that would be affected by the information over the anticipated lifetime of the technology:

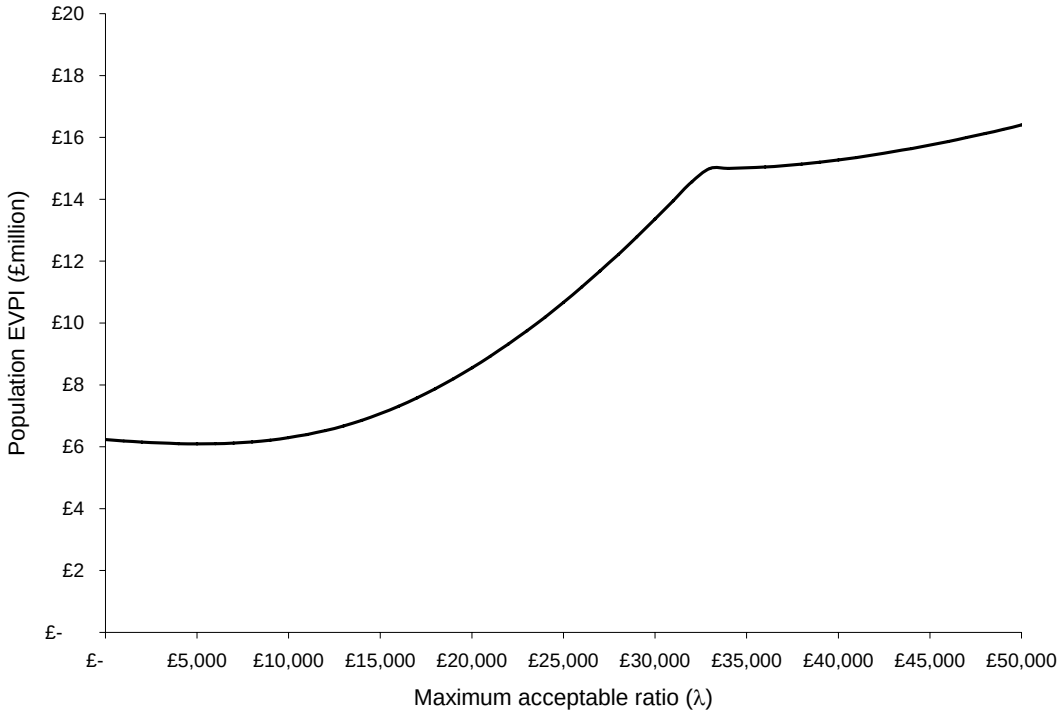
$$EVPI * \sum_{t=1}^{T} \frac{I_t}{(1+r)^t}$$

Where: I = incidence in period, t = period, T= total number of periods for which information from research would be useful, r= discount rate

No details regarding the prevalence and/or incidence of HRPC were identified for the UK in any of the articles considered by the clinical and cost-effectiveness reviews. In the absence of these data we used national mortality statistics for all patients with prostate cancer in England and Wales (9,161)[2] and an assumption that only 30% of these patients would require and be eligible for docetaxel plus prednisone/prednisolone. This gives an annual population of 2,748 patients for whom this decision is relevant. In addition, the time horizon was set to be 1.5 years based on the current timelines surrounding the forthcoming NICE appraisal of Atrasentan.

Figure 10 illustrates the EVPI for the population (as described above) based on analysis 2. The EVPI curve increases over the full range of values for the maximum acceptable ratio, with a local maximum occurring at the value that corresponds to the ICER (£32,706). Given a maximum acceptable ratios of £20,000, £30,000 and £40,000 the EVPI for the population are £8.55 million, £13.36 million and £15.27 million respectively.

Figure 10: Population expected value of perfect information (EVPI) for the decision between D+P (3-weekly), M+P, P, D+P (weekly), D+E, D+E+P (70), D+E+P (35) and M+P+C



6.8. Budget impact analysis

In order to estimate the budget impact of the economic model recommendations we have considered the additional costs associated with the use of docetaxel plus prednisone/prednisolone compared to current NHS practice. Since the use of chemotherapy (e.g. mitoxantrone) appears to dominate prednisone/prednisone alone (and hence incurs lower NHS costs), we have based the main estimates on an evaluation of the costs of switching treatment from the use of mitoxantrone plus prednisone/prednisolone.

Based on a similar approach to that used to quantify the size of the population used in the value of information analysis, we have assumed an annual population of 2,748. If all patients were to receive docetaxel plus prednisone/prednisolone, the total additional cost to the NHS would be approximately £13.88 million (i.e. an additional cost of £5,049 per patient). This figure represents an upper bound on the potential budgetary projections, since not all patients will currently be receiving chemotherapy.

A similar calculation based on the costs of switching from the use of prednisone/prednisolone results in a total additional cost to the NHS of £12.79 million (based on an additional cost of £4,655). Hence, the budget impact will be in the range £12.79 to £13.88 million depending on the proportion of patients currently receiving these treatments.

6.9. Conclusions

The models presented here indicate that docetaxel plus prednisone/prednisolone appears cost-effective compared to other chemotherapy and non-chemotherapy regimens, as long as the NHS is willing to pay at least £32,706 per QALY. The use of prednisone appears to be dominated by mitoxantrone plus prednisone and hence the cost-effectiveness of docetaxel plus prednisone/prednisolone is most appropriately informed by a comparison against this. The estimate of the ICER remained robust between the two models considered despite the differences in the range of comparators considered in each model. However, the incorporation of a fuller range of potential comparators, as modelled in Analysis 2, led to an increase in the decision uncertainty as illustrated in the cost-effectiveness acceptability curves and frontier. The formal quantification of this decision uncertainty is illustrated in the value of information analysis.

A range of sensitivity analyses were undertaken to test the robustness of the model to alternative assumptions regarding discount rates, quality of life estimates and the impact of side effects. The ICER associated with D+P (3-weekly) remained fairly robust to these variations with estimates ranging from £28,019 to £33,298 per QALY.

7. Discussion

7.1. Clinical evaluation

We identified one trial that directly assessed the intervention under consideration: docetaxel plus prednisone; this was in comparison with mitoxantrone plus prednisone (TAX 327). No other trials were found that assessed the clinical effectiveness of docetaxel plus prednisone.

The results of this trial showed statistically significant improvements with 3-weekly docetaxel plus prednisone compared with mitoxantrone plus prednisone, in terms of overall survival, quality of life, pain response, and PSA decline. Response rate was higher for the 3-weekly docetaxel plus prednisone group than the mitoxantrone plus prednisone group, but this difference was not statistically significant. The improved outcomes for docetaxel plus prednisone were associated with more grade 3-4 adverse events; however, this had no detrimental effect on quality of life, which was also significantly improved in the 3-weekly docetaxel group. Progression-free survival was not assessed in this trial. This was a large, well-conducted RCT and the results are likely to be reliable, however the lack of other studies available for the evaluation of the efficacy of docetaxel plus prednisone is a limitation of this review.

Since docetaxel plus prednisone has only been directly compared with mitoxantrone plus prednisone, we considered additional evidence which would enable a comparison of docetaxel plus prednisone with other chemotherapy-based treatments and best supportive care. Therefore, we searched for other treatments that were compared with mitoxantrone plus a corticosteroid, in order to allow a comparison across the full range of relevant treatment options. We found three trials that compared other chemotherapy regimens with mitoxantrone plus prednisone: one trial that compared mitoxantrone plus prednisone with docetaxel plus prednisone plus estramustine; one trial that compared mitoxantrone plus prednisone with docetaxel plus estramustine; and one trial that compared mitoxantrone plus prednisone with mitoxantrone plus prednisone plus clodronate. Both treatments that included docetaxel were superior to mitoxantrone plus prednisone in terms of overall survival (although the difference was not statistically significant for docetaxel plus prednisone plus estramustine), response rate (although the difference was not statistically significant for docetaxel plus

estramustine), and progression-free survival (although this was only assessed for docetaxel plus estramustine in comparison with mitoxantrone plus prednisone). Docetaxel plus estramustine was associated with more adverse events, compared with mitoxantrone plus prednisone. No significant differences were found between mitoxantrone plus prednisone plus clodronate and mitoxantrone plus prednisone without clodronate. A mixed treatment comparison has been presented incorporating these drug combinations. However, since we only searched for trials which included docetaxel plus prednisone/prednisolone or mitoxantrone plus a corticosteroid as one of the treatment arms, this should be interpreted with caution as the search strategy did not include searches for all available evidence that could inform this comparison. It is possible that other trials may exist that could inform this comparison, but which did not meet our review inclusion criteria. Only the results for overall survival were presented in the mixed treatment comparison, this is because the definitions and measurements of the other outcomes varied across the trials and thus it is impossible to make any comparisons between trials for any other outcome, as discussed previously.

In addition, we found three trials that compared mitoxantrone plus a corticosteroid with best supportive care, in the form of corticosteroids. No trials were identified that compared other forms of best supportive care with mitoxantrone plus a corticosteroid. Two of the trials used prednisone (5 mg twice daily) as the comparator, while one compared mitoxantrone plus hydrocortisone with hydrocortisone (40 mg given in two divided doses daily). One of the trials comparing mitoxantrone plus a corticosteroid with a corticosteroid included men with asymptomatic mHRPC, another included men with symptomatic mHRPC, while the third study included all men with progressive mHRPC. This difference in disease severity between patients included in the trials may have affected the results, as mitoxantrone was more effective in the trial of patients with symptoms of pain (CCI-NOV22) and least effective in the trial that only included asymptomatic patients.

In addition to the differences in population, one trial allowed patients to cross over during the trial, this resulted in 50 out of 81 patients randomised to prednisone receiving additional mitoxantrone; the other two trials did not allow crossovers.

Including crossovers in intention to treat analyses can result in 'dilution' of the true effects of a treatment, as patients are analysed as randomised. However, in this case the study that allowed crossovers had a stronger treatment effect in favour of mitoxantrone plus prednisone than the two studies that did not allow crossovers.

The combined result of these three trials showed very little difference between mitoxantrone plus corticosteroids compared with corticosteroids alone in terms of overall survival (HR=0.99 [95% CI: 0.82, 1.20]). Other outcomes could not be pooled because they were measured differently in the three trials. However, in the two studies that measured health-related quality of life and pain responses, the mitoxantrone groups had statistically significant improvements compared with the corticosteroid groups. Due to the limited follow-up for these outcomes these benefits should not be overstated.

In order to complete the network and assess the efficacy of docetaxel plus prednisone compared to best supportive care (corticosteroids), it is possible to perform a formal adjusted indirect comparison as proposed by Bucher et al.[63] This method is the most appropriate as it conserves the power of randomisation and hence protects data from being subject to the biases associated with observational studies. There are several assumptions and issues, such as the internal validity and similarity of the trials to be included in the indirect comparison, which must be considered first. However, evidence presented by Song et al.,[62] suggests that in the absence of a direct trial and after careful consideration of the issues, then it is unlikely that the results of an indirect comparison will differ significantly from the results of a direct trial. Thus there is value in performing such adjusted indirect comparisons.

Therefore, an additional adjusted indirect comparison was performed to estimate the relative efficacy of docetaxel plus prednisone versus corticosteroids. The results of the indirect comparison showed that docetaxel plus prednisone seems to be superior to prednisone alone in terms of overall survival. However, this is based on an indirect comparison using one good quality trial comparing docetaxel plus prednisone with mitoxantrone plus prednisone (TAX 327) and three trials comparing mitoxantrone plus corticosteroids with corticosteroids, that differed in terms of patient population

and methodology. Therefore, the results of this indirect comparison need to be interpreted with caution. The TAX 327 trial included both symptomatic and asymptomatic patients, therefore the population is most similar to that in the CALGB 9182 trial. All patients included in the indirect comparison had to have progressive mHRPC, therefore, can be regarded as a relatively homogenous subset of patients healthy enough to receive chemotherapy. However, if the indirect comparison had been performed using only the CALGB 9182 trial, the results would have been different. The CCI-NOV22 trial was the most similar to TAX 327 in terms of treatment and the fact that crossovers were allowed in both trials. The indirect comparison was repeated using only this trial, the results of which showed that the estimated HR using the pooled treatment effect was more conservative.

In summary, a direct comparison of docetaxel plus prednisone versus mitoxantrone plus prednisone in an open-label randomised trial showed statistically significant higher overall survival for docetaxel plus prednisone. Other outcomes, such as response rate, quality of life, pain, and PSA decline were also in favour of docetaxel plus prednisone. These improved outcomes were associated with more grade 3-4 adverse events; however, this had no detrimental effect on quality of life, which was also significantly improved in the docetaxel plus prednisone group. Two other chemotherapy regimens were found that included docetaxel: docetaxel plus estramustine and docetaxel plus prednisone plus estramustine, both were superior to mitoxantrone plus prednisone in terms of overall survival, response rate, and progression-free survival. The only other chemotherapy regime we found that did not include docetaxel: mitoxantrone plus prednisone plus clodronate, showed no significant differences in comparison with mitoxantrone plus prednisone. Our review of the data suggests that docetaxel plus prednisone is the most effective treatment for men with mHRPC.

7.2. Economic evaluation

Only one published study met the inclusion criteria for the cost-effectiveness review. In addition, a separate submission was received from Sanofi-Aventis. Both of these studies were based on cost-effectiveness analyses undertaken alongside separate randomised controlled trials. Hence, the range of comparators included in both was

constrained to those evaluated in each of these trials. The published study and manufacturer's submission were assessed, and a new model was developed to address the limitations identified in these sources and to provide a direct comparison of the full range of possible strategies that are potentially relevant to the NHS. The model explored a range of uncertainties and sources of variability that were not fully addressed in existing data sources. In particular, the lack of quality-adjustment in the outcome measure used in the submission by Sanofi-Aventis was addressed using a separate systematic review of external evidence reporting on the quality of life in patients with mHRPC in order to estimate QALYs.

The analyses presented here indicate that mitoxantrone plus prednisone/prednisolone dominates the use of prednisone/prednisolone alone. For the purposes of assessing the incremental cost-effectiveness of docetaxel (3-weekly) plus prednisone/prednisolone, the appropriate comparator for these estimates is therefore mitoxantrone plus prednisone/prednisolone. The economic model presented in this report demonstrates that docetaxel (3-weekly) plus prednisone/prednisolone appears cost-effective, in patients with mHRPC, provided the NHS is willing to pay £32,706 per QALY. A series of sensitivity analyses were undertaken to determine the robustness of this result to alternative assumptions related to discount rates and the estimates of quality of life applied in the model. The ICER associated with D+P (3-weekly) remained fairly robust to these variations with estimates ranging from £28,019 to £33,298 per QALY.

Central to the development of the economic model was the need to consider the full range of comparators that are likely to be relevant from an NHS perspective. Hence, it was necessary to consider a broader range of comparators than considered in either of the two studies considered in the review of cost-effectiveness evidence. In the absence of direct ('head-to-head') comparisons for the full range of comparators considered it was necessary to synthesise effectiveness data using indirect treatment comparisons. The strength of this approach is that it allows consideration of the complete evidence base and facilitates a valid comparison of the full range of treatment strategies. However, it must also be recognised that when indirect evidence is used as the basis for the assessment of relative treatment effects, it is not possible to rule out the

introduction of bias, and hence the results should be interpreted accordingly. Although concerns are often raised regarding the use of indirect approaches in establishing the cost-effectiveness of particular interventions, it is important to recognise that these approaches are necessary in order to provide a simultaneous assessment of the full range of potential comparators. It is only through such approaches that the potential inconsistencies that could be introduced by a series of separate comparisons (i.e. assessing the cost-effectiveness of those interventions considered in individual RCTs) can be avoided. As a result this avoids the inevitable difficulties faced by a decision maker in making a single recommendation based on multiple sources of evidence. Furthermore, the analytic approach used to estimate the indirect estimates for the treatment effects considered are based on similar assumptions as applied in standard meta-analysis.

While the cost-effectiveness model addressed a number of the major limitations considered in the review of the submission by Sanofi-Aventis, this model also has several potential limitations that need to be considered in conjunction with the main results. First, it should be recognised that the model did not attempt to quantify any additional palliative benefits conferred by any of the chemotherapeutic regimens (over and above the increased benefits derived from gains in survival). By not considering these benefits the cost-effectiveness estimate from the model should be taken to be conservative. It is difficult to assess the size of these potential palliative benefits due to the limitations noted in the effectiveness review of existing QoL studies, and whether these would be sufficient to offset any potential decrements associated with the emergence of major side-effects. The problems encountered in this part of the analysis emphasise the importance of assessing QoL, using a generic measure which can be applied in cost-effectiveness analyses, as part of any future study in this area.

In the absence of patient level data it was not possible to conduct a detailed analysis of the resource use and costs associated with the component parts of the follow-up costs considered (i.e. the management of adverse events, subsequent chemotherapies and palliative care). As a result, costs were modelled using aggregate data and as such the potential impact of the different treatments on these separate components could not be reflected in the subsequent analyses. In addition, resource use and cost data for

a number of the treatment regimens considered were not available from any source considered. Hence, we assumed that the subsequent follow-up costs for docetaxel regimens would be similar. In the absence of comparative data it is difficult to assess the robustness of this approach. In addition, UK specific cost data for the follow-up costs associated with treatment with prednisone/prednisolone alone were not available. Consequently we assumed that a similar relationship would hold between the follow-up costs as was reported for the comparison of mitoxantrone plus prednisone versus prednisone/prednisolone alone in the study by Bloomfield et al. It is unclear how generalisable the results of this study are to the NHS setting given the potential for differences in the subsequent management of patients with mHRPC between the two settings. However, since the approach applied was based upon modelling the relative difference in costs (as opposed to using the absolute cost estimates) and applying this to UK specific follow-up costs this impact will be minimised. Furthermore, we quantified the uncertainty in this relationship using a probabilistic approach.

7.3. Recommendations for research

- At the time of this assessment there were ongoing trials of docetaxel, in which docetaxel was the standard treatment arm and used in combination with other therapies as the experimental arm(s) (described in section 4.1), therefore, it is difficult to make any recommendations for further research of docetaxel.
- Future research should include the assessment of quality of life associated with different treatments including adverse events of treatment, using generic quality of life instruments, which are suitable for the purposes of cost-effectiveness analyses.

8. Conclusions

Evidence from one well-conducted RCT suggests that docetaxel plus prednisone is superior to mitoxantrone plus prednisone, in terms of overall survival, quality of life response, pain response, and PSA decline.

The combined result of three trials that assessed mitoxonatrone plus a corticosteroid versus a corticosteroid showed very little difference between the two treatment arms

in terms of overall survival. Other outcomes could not be pooled because they were measured differently in the three trials. However, in the two studies that measured health-related quality of life and pain responses, the mitoxantrone groups had statistically significant improvements compared with the corticosteroid groups.

Docetaxel plus prednisone seems to be superior to a corticosteroid alone in terms of overall survival. However, this is based on an indirect comparison; therefore, the results need to be interpreted with caution.

Our review of the data suggests that docetaxel plus prednisone is the most effective treatment for men with mHRPC.

The results of the cost-effectiveness analysis suggest that docetaxel plus prednisone/prednisolone is cost-effective compared to other chemotherapy and non-chemotherapy regimens, as long as the NHS is willing to pay at least £32,706 per QALY. The use of prednisone appears to be dominated by mitoxantrone plus prednisone and hence the cost-effectiveness of docetaxel plus prednisone/prednisolone is most appropriately informed by a comparison against mitoxantrone plus prednisone. The estimate of the ICER remained robust based on separate analyses involving a range of alternative comparisons. Sensitivity analyses demonstrated that the main results appeared fairly robust to alternative assumptions related to the choice of discount rate and the quality of life assumptions. The ICER of docetaxel plus prednisone/prednisolone ranged from £28,019 to £33,298 in these additional analyses. Since these results do not incorporate any additional palliative benefits (i.e. QALY gains) that may accrue to use of docetaxel these estimates may be conservative.

9. References

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10. Appendices

Appendix 10.1. Literature searches

10.1.1. Clinical effectiveness

Searching for the clinical effectiveness component of this review was addressed by two separate searches to identify:

- Reports of RCTs of Docetaxel in the treatment of HRPC
- Reports of RCTs of Mitoxantrone in the treatment of HRPC

The initial strategy was developed for Medline and adapted, with relevant subject indexing, to run on the other databases.

Medline (OVID Online - http://www.ovid.com/)
1966 to March Week 4 2005

Limits:

- No date limits were applied
- Animal-only studies were excluded
- No study design limits or language limits were applied

Strategy for Docetaxel
This search retrieved 169 references.

1. prostatic neoplasms/
2. ((prostate or prostatic) adj2 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or tumour$ or tumor$)).ti,ab.
3. 1 or 2
4. animals/
5. human/
6. 4 not (4 and 5)
7. 3 not 6
8. Docetaxel.ti,ab.
9. Asodecel.ti,ab.
10. Dolectran.ti,ab.
11. Donataxel.ti,ab.
12. Doxetal.ti,ab.
13. Doxmil.ti,ab.
14. Neocel.ti,ab.
15. Plustaxano.ti,ab.
16. Texot.ti,ab.
17. Trazoteva.ti,ab.
18. Trixotene.ti,ab.
19. Daxotel.ti,ab.
20. NSC-628503.mp.
21. RP-56976.mp.
22. 114977-28-5.mp.
23. L01cd02.mp.
24. taxotere.mp.

25. or/8-24
26. 7 and 25

Strategy for Mitoxantrone
This search retrieved 118 references.

1. prostatic neoplasms/
2. ((prostate or prostatic) adj2 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or tumour$ or tumor$)).ti,ab.
3. 1 or 2
4. animals/
5. human/
6. 4 not (4 and 5)
7. 3 not 6
8. Mitoxantrone.mp.
9. Mitoxantrone/
10. Mitozantrone.ti,ab.
11. Mitoxantrone hydrochloride.ti,ab.
12. BP 2003.mp.
13. USP 27.mp.
14. Novatrone.ti,ab.
15. Onkotrone.ti,ab.
16. Batinel.ti,ab.
17. Micraleve.ti,ab.
18. Mitoxgen.ti,ab.
19. Mitoxmar.ti,ab.
20. Novatron.ti,ab.
21. Misostol.ti,ab.
22. Mitoxal.ti,ab.
23. Neotalem.ti,ab.
24. Genefadrone.ti,ab.
25. Formyxan.ti,ab.
26. Mitroxone.ti,ab.
27. Serotron.ti,ab.
28. Pralifan.ti,ab.
29. CL 232315.mp.
30. DHAD.ti,ab.
31. Dihydroxyanthracenedione dihydrochloride.ti,ab.
32. Hidrocloruro de mitoxantrona.ti,ab.
33. Mitoxantroni hydrochloridum.ti,ab.
34. Mitrozantrone hydrochloride.ti,ab.
35. Nsc 301739.mp.
36. 65271 80 9.mp.
37. 70476 82 3.mp.
38. L01db07.mp.
39. Novantrone.mp.
40. or/8-39
41. 7 and 40

MEDLINE In Process And Other Non-Indexed Citations (Ovid Online – www.ovid.com)
April 01 2005 (Docetaxel) : April 04 2005 (Mitoxantrone)

Limits:

- No date limits were applied
- Animal-only studies were excluded
- No study design limits or language limits were applied

Strategy for Docetaxel
This search retrieved 21 references.

1. prostatic neoplasms/
2. ((prostate or prostatic) adj2 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or tumour$ or tumor$)).ti,ab.
3. 1 or 2
4. animals/
5. human/
6. 4 not (4 and 5)
7. 3 not 6
8. Docetaxel.ti,ab.
9. Asodecel.ti,ab.
10. Dolectran.ti,ab.
11. Donataxel.ti,ab.
12. Doxetal.ti,ab.
13. Doxmil.ti,ab.
14. Neocel.ti,ab.
15. Plustaxano.ti,ab.
16. Texot.ti,ab.
17. Trazoteva.ti,ab.
18. Trixotene.ti,ab.
19. Daxotel.ti,ab.
20. NSC-628503.mp.
21. RP-56976.mp.
22. 114977-28-5.mp.
23. L01cd02.mp.
24. taxotere.mp.
25. or/8-24
26. 7 and 25

Strategy for Mitoxantrone
This search retrieved 11 references.

1. prostatic neoplasms/
2. ((prostate or prostatic) adj2 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or tumour$ or tumor$)).ti,ab.
3. 1 or 2
4. animals/
5. human/

6. 4 not (4 and 5)
7. 3 not 6
8. Mitoxantrone.mp.
9. MITOXANTRONE/
10. Mitozantrone.ti,ab.
11. Mitoxantrone hydrochloride.ti,ab.
12. BP 2003.mp.
13. USP 27.mp.
14. Novatrone.ti,ab.
15. Onkotrone.ti,ab.
16. Batinel.ti,ab.
17. Micraleve.ti,ab.
18. Mitoxgen.ti,ab.
19. Mitoxmar.ti,ab.
20. Novatron.ti,ab.
21. Misostol.ti,ab.
22. Mitoxal.ti,ab.
23. Neotalem.ti,ab.
24. Genefadrone.ti,ab.
25. Formyxan.ti,ab.
26. Mitroxone.ti,ab.
27. Serotron.ti,ab.
28. Pralifan.ti,ab.
29. CL 232315.mp.
30. DHAD.ti,ab.
31. Dihydroxyanthracenedione dihydrochloride.ti,ab.
32. Hidrocloruro de mitoxantrona.ti,ab.
33. Mitoxantroni hydrochloridum.ti,ab.
34. Mitrozantrone hydrochloride.ti,ab.
35. Nsc 301739.mp.
36. 65271 80 9.mp.
37. 70476 82 3.mp.
38. L01db07.mp.
39. Novantrone.mp.
40. or/8-39
41. 7 and 40

EMBASE (OVID Online - http://www.ovid.com/)
1980 to 2005 week 14

Limits:

- No date limits were applied
- Animal-only studies were excluded
- No study design limits or language limits were applied

Strategy for Docetaxel
This search retrieved 212 references.

1. Prostatic Intraepithelial Neoplasia/

2. ((prostate or prostatic) adj2 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or tumour$ or tumor$)).ti,ab.
3. 1 or 2
4. animal/
5. human/
6. 4 not (4 and 5)
7. 3 not 6
8. Docetaxel.ti,ab.
9. Asodecel.ti,ab.
10. Dolectran.ti,ab.
11. Donataxel.ti,ab.
12. Doxetal.ti,ab.
13. Doxmil.ti,ab.
14. Neocel.ti,ab.
15. Plustaxano.ti,ab.
16. Texot.ti,ab.
17. Trazoteva.ti,ab.
18. Trixotene.ti,ab.
19. Daxotel.ti,ab.
20. NSC-628503.mp.
21. RP-56976.mp.
22. 114977-28-5.mp.
23. L01cd02.mp.
24. taxotere.mp.
25. taxotere/ or docetaxel/
26. or/8-25
27. 26 and 7

Strategy for Mitoxantrone
This search retrieved 403 references.

1. Prostatic Intraepithelial Neoplasia.mp.
2. ((prostate or prostatic) adj2 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or tumour$ or tumor$)).ti,ab.
3. 1 or 2
4. animal/
5. human/
6. 4 not (4 and 5)
7. 3 not 6
8. Mitoxantrone.mp.
9. Mitoxantrone/
10. Mitozantrone.ti,ab.
11. Mitoxantrone hydrochloride.ti,ab.
12. BP 2003.mp.
13. USP 27.mp.
14. Novatrone.ti,ab.
15. Onkotrone.ti,ab.
16. Batinel.ti,ab.
17. Micraleve.ti,ab.

18. Mitoxgen.ti,ab.
19. Mitoxmar.ti,ab.
20. Novatron.ti,ab.
21. Misostol.ti,ab.
22. Mitoxal.ti,ab.
23. Neotalem.ti,ab.
24. Genefadrone.ti,ab.
25. Formyxan.ti,ab.
26. Mitroxone.ti,ab.
27. Serotron.ti,ab.
28. Pralifan.ti,ab.
29. CL 232315.mp.
30. DHAD.ti,ab.
31. Dihydroxyanthracenedione dihydrochloride.ti,ab.
32. Hidrocloruro de mitoxantrona.ti,ab.
33. Mitoxantroni hydrochloridum.ti,ab.
34. Mitrozantrone hydrochloride.ti,ab.
35. Nsc 301739.mp.
36. 65271 80 9.mp.
37. 70476 82 3.mp.
38. L01db07.mp.
39. Novantrone.mp.
40. or/8-39
41. 7 and 40

Cochrane Central Register of Controlled Trials (CENTRAL) and The Cochrane Database of Systematic Reviews (CDSR) (The Cochrane Library on cd-rom)
2005 Issue 1

Limits:

- No date limits were applied
- No study design limits or language limits were applied

Strategy for Docetaxel
This search retrieved 10 references from CENTRAL and 0 references from CDSR.

1. PROSTATIC NEOPLASMS (MeSH – single term)
2. (prostate near neoplasm*)
3. (prostate near cancer*)
4. (prostate near carninoma*)
5. (prostate near adenocarcinoma*)
6. (prostate near tumor*)
7. (prostate near tumour*)
8. (prostatic near neoplasm*)
9. (prostatic near cancer*)
10. (prostatic near carninoma*)
11. (prostatic near adenocarcinoma*)
12. (prostatic near tumor*)
13. (prostatic near tumour*)

14. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13)
15. docetaxel
16. taxotere
17. asodecel
18. dolectran
19. donataxel
20. doxetal
21. doxmil
22. neocel
23. plustaxano
24. texot
25. trazoteva
26. trixotene
27. daxotel
28. nsc-628503
29. rp-56976
30. 114977-28-5
31. l01cd02
32. taxotere
33. (#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32)
34. (#14 and #33)

Strategy for Mitoxantrone
This search retrieved 20 references from CENTRAL and 1 reference from CDSR.

1. PROSTATIC NEOPLASMS (MeSH – single term)
2. (prostate near neoplasm*)
3. (prostate near cancer*)
4. (prostate near carninoma*)
5. (prostate near adenocarcinoma*)
6. (prostate near tumor*)
7. (prostate near tumour*)
8. (prostatic near neoplasm*)
9. (prostatic near cancer*)
10. (prostatic near carninoma*)
11. (prostatic near adenocarcinoma*)
12. (prostatic near tumor*)
13. (prostatic near tumour*)
14. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13)
15. mitoxantrone
16. MITOXANTRONE (MeSH – single term)
17. mitozantrone
18. (mitoxantrone next hydrochloride)
19. bp-2003
20. usp-27
21. novatrone
22. onkotrone
23. batinel

24. micraleve
25. mitoxgen
26. mitoxmar
27. novatron
28. misostol
29. mitoxal
30. neotalem
31. genefadrone
32. formyxan
33. mitroxone
34. serotron
35. pralifan
36. cl-232315
37. dhad
38. (dihydroxyanthracenedione next dihydrochloride)
39. (hidrocloruro next de next mitoxantrona)
40. (mitoxantroni next hydrochloridum)
41. (mitrozantrone next hydrochloride)
42. nsc-301739
43. 65271-80-9
44. 70476-82-3
45. l01db07
46. novantrone
47. (#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46)
48. (#14 and #47)

National Research Register (NRR) (cd-rom)
2005 Issue 1

Limits:

- No date limits were applied
- No study design limits or language limits were applied

Strategy for Docetaxel
This search retrieved 6 references.

1. PROSTATIC NEOPLASMS (MeSH – single term)
2. (prostate near neoplasm*)
3. (prostate near cancer*)
4. (prostate near carninoma*)
5. (prostate near adenocarcinoma*)
6. (prostate near tumor*)
7. (prostate near tumour*)
8. (prostatic near neoplasm*)
9. (prostatic near cancer*)
10. (prostatic near carninoma*)
11. (prostatic near adenocarcinoma*)

12. (prostatic near tumor*)
13. (prostatic near tumour*)
14. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13)
15. docetaxel
16. taxotere
17. asodecel
18. dolectran
19. donataxel
20. doxetal
21. doxmil
22. neocel
23. plustaxano
24. texot
25. trazoteva
26. trixotene
27. daxotel
28. nsc-628503
29. rp-56976
30. 114977-28-5
31. l01cd02
32. taxotere
33. (#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32)
34. (#14 and #33)

Strategy for Mitoxantrone
This search retrieved 9 references.

1. PROSTATIC NEOPLASMS (MeSH – single term)
2. (prostate near neoplasm*)
3. (prostate near cancer*)
4. (prostate near carninoma*)
5. (prostate near adenocarcinoma*)
6. (prostate near tumor*)
7. (prostate near tumour*)
8. (prostatic near neoplasm*)
9. (prostatic near cancer*)
10. (prostatic near carninoma*)
11. (prostatic near adenocarcinoma*)
12. (prostatic near tumor*)
13. (prostatic near tumour*)
14. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13)
15. mitoxantrone
16. MITOXANTRONE (MeSH – single term)
17. mitozantrone
18. (mitoxantrone next hydrochloride)
19. bp-2003
20. usp-27
21. novatrone

22. onkotrone
23. batinel
24. micraleve
25. mitoxgen
26. mitoxmar
27. novatron
28. misostol
29. mitoxal
30. neotalem
31. genefadrone
32. formyxan
33. mitroxone
34. serotron
35. pralifan
36. cl-232315
37. dhad
38. (dihydroxyanthracenedione next dihydrochloride)
39. (hidrocloruro next de next mitoxantrona)
40. (mitoxantroni next hydrochloridum)
41. (mitrozantrone next hydrochloride)
42. nsc-301739
43. 65271-80-9
44. 70476-82-3
45. l01db07
46. novantrone
47. (#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46)
48. (#14 and #47)

Health Technology Assessment Database (HTA), NHS Economic Evaluation Database (NHS EED) and Database of Abstracts of Reviews of Effects (DARE) (CRD administration database)
Searched: 5th April 2005

Limits:

- No date limits were applied
- No study design limits or language limits were applied

Strategy for Docetaxel
This search retrieved 3 references from HTA, 0 references from NHS EED and 12 references from DARE.

1. prostate(2w)neoplasm$
2. prostate(2w)cancer$
3. prostate(2w)carcinoma$
4. prostate(2w)adenocarcinoma$
5. prostate(2w)tumour$
6. prostate(2w)tumor$

7. prostatic(2w)neoplasm$
8. prostatic(2w)cancer$
9. prostatic(2w)carcinoma$
10. prostatic(2w)adenocarcinoma$
11. prostatic(2w)tumour$
12. prostatic(2w)tumor$
13. s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12
14. Docetaxel
15. Asodecel
16. Dolectran
17. Donataxel
18. Doxetal
19. Doxmil
20. Neocel
21. Plustaxano
22. Texot
23. Trazoteva
24. Trixotene
25. Daxotel
26. taxotere
27. s14 or s15 or s16 or s17 or s18 or s19 or s20 or s21 or s22 or s23 or s24 or s25 or s26
28. s27 and s13

Strategy for Mitoxantrone
This search retrieved 0 references from HTA, 4 references from NHS EED and 8 references from DARE.

1. prostate(2w)neoplasm$
2. prostate(2w)cancer$
3. prostate(2w)carcinoma$
4. prostate(2w)adenocarcinoma$
5. prostate(2w)tumour$
6. prostate(2w)tumor$
7. prostatic(2w)neoplasm$
8. prostatic(2w)cancer$
9. prostatic(2w)carcinoma$
10. prostatic(2w)adenocarcinoma$
11. prostatic(2w)tumour$
12. prostatic(2w)tumor$
13. s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12
14. Mitoxantrone
15. Mitozantrone
16. Mitoxantrone(w)hydrochloride
17. BP(w)2003
18. USP(w)27
19. Novatrone
20. Onkotrone
21. Batinel

22. Micraleve
23. Mitoxgen
24. Mitoxmar
25. Novatron
26. Misostol
27. Mitoxal
28. Neotalem
29. Genefadrone
30. Formyxan
31. Mitroxone
32. Serotron
33. Pralifan
34. DHAD
35. Dihydroxyanthracenedione dihydrochloride
36. Hidrocloruro(w)de(w)mitoxantrona
37. Mitoxantroni(w)hydrochloridum
38. Mitrozantrone(w)hydrochloride
39. Novantrone
40. s14 or s15 or s16 or s17 or s18 or s19 or s20 or s21 or s22 or s23 or s24 or s25 or s26 or s27 or s28 or s29 or s30 or s31 or s32 or s33 or s34 or s35 or s36 or s37 or s38 or s39
41. s40 and s13

Cumulative Index to Nursing & Allied Health Literature (CINAHL) (Ovid Online – www.ovid.com)
1982 to April Week 1 2005

Limits:

- No date limits were applied
- No study design limits or language limits were applied

Strategy for Docetaxel
This search retrieved 4 references.

1 prostatic neoplasms/
2 ((prostate or prostatic) adj2 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or tumour$ or tumor$)).ti,ab.
3 1 or 2
4 Docetaxel.ti,ab.
5 Asodecel.ti,ab.
6 Dolectran.ti,ab.
7 Donataxel.ti,ab.
8 Doxetal.ti,ab.
9 Doxmil.ti,ab.
10 Neocel.ti,ab.
11 Plustaxano.ti,ab.
12 Texot.ti,ab.
13 Trazoteva.ti,ab.
14 Trixotene.ti,ab.

15 Daxotel.ti,ab.
16 NSC-628503.mp.
17 RP-56976.mp.
18 114977-28-5.mp.
19 L01cd02.mp.
20 taxotere.mp.
21 or/4-20
22 3 and 21

Strategy for Mitoxantrone
This search retrieved 5 references.

1. prostatic neoplasms/
2. ((prostate or prostatic) adj2 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or tumour$ or tumor$)).ti,ab.
3. 1 or 2
4. Mitoxantrone.mp.
5. MITOXANTRONE/
6. Mitozantrone.ti,ab.
7. Mitoxantrone hydrochloride.ti,ab.
8. BP 2003.mp.
9. USP 27.mp.
10. Novatrone.ti,ab.
11. Onkotrone.ti,ab.
12. Batinel.ti,ab.
13. Micraleve.ti,ab.
14. Mitoxgen.ti,ab.
15. Mitoxmar.ti,ab.
16. Novatron.ti,ab.
17. Misostol.ti,ab.
18. Mitoxal.ti,ab.
19. Neotalem.ti,ab.
20. Genefadrone.ti,ab.
21. Formyxan.ti,ab.
22. Mitroxone.ti,ab.
23. Serotron.ti,ab.
24. Pralifan.ti,ab.
25. CL 232315.mp.
26. DHAD.ti,ab.
27. Dihydroxyanthracenedione dihydrochloride.ti,ab.
28. Hidrocloruro de mitoxantrona.ti,ab.
29. Mitoxantroni hydrochloridum.ti,ab.
30. Mitrozantrone hydrochloride.ti,ab.
31. Nsc 301739.mp.
32. 65271 80 9.mp.
33. 70476 82 3.mp.
34. L01db07.mp.
35. Novantrone.mp.
36. or/4-35

37. 3 and 36

Health Management Information Consortium (HMIC) (Ovid Online – www.ovid.com)
March 2005

Limits:

- No date limits were applied
- Animal-only studies were excluded
- No study design limits or language limits were applied

Strategy for Docetaxel
This search retrieved 0 references.

1. prostate cancer/
2. ((prostate or prostatic) adj2 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or tumour$ or tumor$)).ti,ab.
3. 1 or 2
4. animals/
5. people/
6. 4 not (4 and 5)
7. 3 not 6
8. Docetaxel.ti,ab.
9. Asodecel.ti,ab.
10. Dolectran.ti,ab.
11. Donataxel.ti,ab.
12. Doxetal.ti,ab.
13. Doxmil.ti,ab.
14. Neocel.ti,ab.
15. Plustaxano.ti,ab.
16. Texot.ti,ab.
17. Trazoteva.ti,ab.
18. Trixotene.ti,ab.
19. Daxotel.ti,ab.
20. NSC-628503.mp.
21. RP-56976.mp.
22. 114977-28-5.mp.
23. L01cd02.mp.
24. taxotere.mp.
25. or/8-24
26. 7 and 25

Strategy for Mitoxantrone
This search retrieved 0 references.

1. prostate cancer/
2. ((prostate or prostatic) adj2 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or tumour$ or tumor$)).ti,ab.
3. 1 or 2

4. animals/
5. people/
6. 4 not (4 and 5)
7. 3 not 6
8. Mitoxantrone.mp.
9. Mitozantrone.ti,ab.
10. Mitoxantrone hydrochloride.ti,ab.
11. BP 2003.mp.
12. USP 27.mp.
13. Novatrone.ti,ab.
14. Onkotrone.ti,ab.
15. Batinel.ti,ab.
16. Micraleve.ti,ab.
17. Mitoxgen.ti,ab.
18. Mitoxmar.ti,ab.
19. Novatron.ti,ab.
20. Misostol.ti,ab.
21. Mitoxal.ti,ab.
22. Neotalem.ti,ab.
23. Genefadrone.ti,ab.
24. Formyxan.ti,ab.
25. Mitroxone.ti,ab.
26. Serotron.ti,ab.
27. Pralifan.ti,ab.
28. CL 232315.mp.
29. DHAD.ti,ab.
30. Dihydroxyanthracenedione dihydrochloride.ti,ab.
31. Hidrocloruro de mitoxantrona.ti,ab.
32. Mitoxantroni hydrochloridum.ti,ab.
33. Mitrozantrone hydrochloride.ti,ab.
34. Nsc 301739.mp.
35. 65271 80 9.mp.
36. 70476 82 3.mp.
37. L01db07.mp.
38. Novantrone.mp.
39. or/8-38
40. 7 and 39

ISI Science and Technology Proceedings (ISTP) and Science Citation Index (SCI) (Internet - Web of Knowledge - http://wos.mimas.ac.uk/)
1990-April 1 2005 (ISTP) and 1945 – April 4 2005 (SCI)

Limits:

- No date limits were applied
- No study design limits or language limits were applied

Strategy for Docetaxel
This search retrieved 60 references from ISTP and 284 from SCI.

#1. TS=((prostate or prostatic) SAME (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*))
#2. TS=(Docetaxel)
#3. TS=(Asodecel)
#4. TS=(Dolectran)
#5. TS=(Donataxel)
#6. TS=(Doxetal)
#7. TS=(Doxmil)
#8. TS=(Neocel)
#9. TS=(Plustaxano)
#10. TS=(Texot)
#11. TS=(Trazoteva)
#12. TS=(Trixotene)
#13. TS=(Daxotel)
#14. TS=(taxotere)
#15. TS=(NSC-628503)
#16. TS=(RP-56976)
#17. TS=(114977-28-5)
#18. TS=(L01cd02)
#19. #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
#20. #1 and #19

Strategy for Mitoxantrone
This search retrieved 29 references from ISTP and 199 from SCI.

#1. TS=((prostate or prostatic) SAME (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*))
#2. TS=(Mitoxantrone)
#3. TS=(Mitozantrone)
#4. TS=(Mitoxantrone hydrochloride)
#5. TS=(BP 2003)
#6. TS=(USP 27)
#7. TS=(Novatrone)
#8. TS=(Onkotrone)
#9. TS=(Batinel)
#10. TS=(Micraleve)
#11. TS=(Mitoxgen)
#12. TS=(Mitoxmar)
#13. TS=(Novatron)
#14. TS=(Misostol)
#15. TS=(Mitoxal)
#16. TS=(Neotalem)
#17. TS=(Genefadrone)
#18. TS=(Formyxan)
#19. TS=(Mitroxone)
#20. TS=(Serotron)
#21. TS=(Pralifan)
#22. TS=(CL 232315)

#23. TS=(DHAD)
#24. TS=(Dihydroxyanthracenedione dihydrochloride)
#25. TS=(Hidrocloruro de mitoxantrona)
#26. TS=(Mitoxantroni hydrochloridum)
#27. TS=(Mitrozantrone hydrochloride)
#28. TS=(Nsc 301739)
#29. TS=(65271 80 9)
#30. TS=(70476 82 3)
#31. TS=(L01db07)
#32. TS=(Novantrone)
#33. #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32
#34. #1 and #33

Index to Theses (Internet - http://www.theses.com/)
1716 – 30 March 2005

Limits:

- No date limits were applied
- No study design limits or language limits were applied

Strategy for Docetaxel
This search retrieved 0 references.

Docetaxel or Asodecel or Dolectran or Donataxel or Doxetal or Doxmil or Neocel or Plustaxano or Texot or Trazoteva or Trixotene or Daxotel or NSC-628503 or RP-56976 or 114977-28-5 or L01cd02 or taxotere

Strategy for Mitoxantrone
This search retrieved 0 references.

(prostate or prostatic) and (Mitoxantrone or Mitozantrone or "Mitoxantrone hydrochloride" or "BP 2003" or "USP 27" or Novatrone or Onkotrone or Batinel or Micraleve or Mitoxgen or Mitoxmar or Novatron or Misostol or Mitoxal or Neotalem or Genefadrone or Formyxan or Mitroxone or Serotron or Pralifan or "CL 232315" or DHAD or "Dihydroxyanthracenedione dihydrochloride" or "Hidrocloruro de mitoxantrona" or "Mitoxantroni hydrochloridum" or "Mitrozantrone hydrochloride" or "Nsc 301739" or "65271 80 9" or "70476 82 3" or L01db07 or Novantrone)

SIGLE (SilverPlatter ARC2 – http://www.ovid.com)
1980 – 2004/12

Limits:

- No date limits were applied
- No study design limits or language limits were applied

Strategy for Docetaxel
This search retrieved 0 references.

#1. (prostate or prostatic) near2 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*)
#2. Docetaxel or Asodecel or Dolectran or Donataxel or Doxetal or Doxmil or Neocel or Plustaxano or Texot or Trazoteva or Trixotene or Daxotel or NSC-628503 or RP-56976 or 114977-28-5 or L01cd02 or taxotere
#3. #1 and #2

Strategy for Mitoxantrone
This search retrieved 0 references.

#1. (prostate or prostatic) near2 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*)
#2. Mitoxantrone or Mitozantrone or (Mitoxantrone adj hydrochloride) or (BP adj 2003) or (USP adj 27) or Novatrone or Onkotrone or Batinel or Micraleve or Mitoxgen or Mitoxmar or Novatron or Misostol or Mitoxal or Neotalem or Genefadrone or Formyxan or Mitroxone or Serotron or Pralifan or (CL adj 232315) or DHAD or (Dihydroxyanthracenedione adj dihydrochloride) or Hidrocloruro or (Mitoxantroni adj hydrochloridum) or (Mitrozantrone adj hydrochloride) or (Nsc adj 301739) or (65271 adj 80 adj 9) or (70476 adj 82 adj 3) or L01db07 or Novantrone
#3. #1 and #2

International Cancer Research Portfolio (ICRP) (Internet - http://www.cancerportfolio.org/)
2000-2005
Searched on 7th April 2005

Limits:
- Search was limited to prostate cancer
- No date limits were applied
- Any of the words were searched for in title or abstract

Strategy for Docetaxel
This search retrieved 34 references.

Docetaxel or Asodecel or Dolectran or Donataxel or Doxetal or Doxmil or Neocel or Plustaxano or Texot or Trazoteva or Trixotene or Daxotel or NSC-628503 or RP-56976 or 114977-28-5 or L01cd02 or taxotere

Strategy for Mitoxantrone
This search retrieved 12 references.

Mitoxantrone or Mitozantrone or Mitoxantrone hydrochloride or BP 2003 or USP 27 or Novatrone or Onkotrone or Batinel or Micraleve or Mitoxgen or Mitoxmar or Novatron or Misostol or Mitoxal or Neotalem or Genefadrone or Formyxan or Mitroxone or Serotron or Pralifan or CL 232315 or DHAD or Dihydroxyanthracenedione dihydrochloride or Hidrocloruro or Mitoxantroni

hydrochloridum or Mitrozantrone hydrochloride or Nsc 301739 or 65271 80 9 or 70476 82 3 or L01db07 or Novantrone

BIOSIS Previews and Inside Conferences (DialogLink - http://www.dialog.com/)
BIOSIS – 1969 - 2005 April week1. Inside Conferences – 1993 - 2005 April week 1

Limits:

- No date limits were applied
- No study design limits or language limits were applied

Strategy for Docetaxel
This search retrieved 193 references from BIOSIS and 13 references from Inside Conferences.

1. (prostate or prostatic)3N(neoplasm? or cancer? or carcinoma? or adenocarcinoma? or tumour? or tumor?)
2. Docetaxel
3. Asodecel
4. Dolectran
5. Donataxel
6. Doxetal
7. Doxmil
8. Neocel
9. Plustaxano
10. Texot
11. Trazoteva
12. Trixotene
13. Daxotel
14. taxotere
15. s2:s14
16. s1 and s15

Strategy for Mitoxantrone
This search retrieved 123 references from BIOSIS and 6 references from Inside Conferences.

1. (prostate or prostatic)(3N)(neoplasm? or cancer? or carcinoma? or adenocarcinoma? or tumour? or tumor?)
2. Mitoxantrone
3. Mitozantrone
4. Mitoxantrone(W)hydrochloride
5. BP(W)2003
6. USP(W)27
7. Novatrone
8. Onkotrone
9. Batinel
10. Micraleve
11. Mitoxgen
12. Mitoxmar

13. Novatron
14. Misostol
15. Mitoxal
16. Neotalem
17. Genefadrone
18. Formyxan
19. Mitroxone
20. Serotron
21. Pralifan
22. CL(W)232315
23. DHAD
24. Dihydroxyanthracenedione(W)dihydrochloride
25. Hidrocloruro(W)de(W)mitoxantrona
26. Mitoxantroni(W)hydrochloridum
27. Mitrozantrone(W)hydrochloride
28. Nsc(W)301739
29. 65271(W)80(W)9
30. 70476(W)82(W)3
31. L01db07
32. Novantrone
33. s2:s32
34. s1 and s33

National Cancer Institute Clinical Trials PDQ (Internet http://www.cancer.gov/Search/SearchClinicalTrialsAdvanced.aspx)
Searched on 8th April 2005

Limits:

- Search was limited to prostate cancer
- Search was limited to treatment and supportive care
- No date limits were applied
- Any of the words were searched for
- Both active and closed trials were searched for

Strategy for Docetaxel
This search retrieved 50 references.

docetaxel; asodecel; dolectran; donataxel; doxetal; doxmil; neocel; plustaxano; texot; trazoteva; trixotene; daxotel; taxotere

Strategy for Mitoxantrone
This search retrieved 19 references.

mitozantrone; mitoxantrone; bp 2003; usp 27; novatrone; onkotrone; batinel; micraleve; mitoxgen; mitoxmar; novatron; misostol; mitoxal; neotalem; genefadrone; formyxan; mitroxone; serotron; pralifan; cl 232315; dhad; dihydroxyanthracenedione dihydrochloride; hidrocloruro de mitoxantrona; mitoxantroni hydrochloridum; mitrozantrone hydrochloride; nsc 301739; 65271 80 9; 70476 82 3; l01db07; novantrone

American Society of Clinical Oncology (Internet - http://www.asco.org)
Searched on 8th April 2005 for Docetaxel and 11th of April for Mitoxantrone

Limits:

- In response to the limits of the search interface, seaching was done in bits, and dates limited to 2000 - 2005
- Words were searched for in the title only

Strategy for Docetaxel
This search retrieved 113 references.

1. (docetaxel OR asodecel OR doxetal) AND prostate
2. (doxmil OR neocel OR plustaxano) AND prostate
3. (texot OR trazoteva OR trixotene) AND prostate
4. (dolectran OR donataxel) AND prostate
5. (daxotel OR taxotere) AND prostate
6. (NSC-628503 OR RP-56976) AND prostate
7. (114977-28-5 OR L01cd02) AND prostate

Strategy for Mitoxantrone
This search retrieved 36 references.

1. (mitozantrone OR mitoxantrone) AND prostate
2. (bp 2003 OR usp 27 OR novatrone) AND prostate
3. (onkotrone OR batinel OR micraleve) AND prostate
4. (mitoxgen OR mitoxmar OR novatron) AND prostate
5. (misostol OR mitoxal OR neotalem) AND prostate
6. (genefadrone OR formyxan OR mitroxone) AND prostate
7. (serotron OR pralifan OR cl 232315) AND prostate
8. (dihydroxyanthracenedione) AND prostate
9. (dhad) AND prostate
10. (hidrocloruro de mitoxantrona) AND prostate
11. (mitoxantroni hydrochloridum) AND prostate
12. (mitrozantrone hydrochloride) AND prostate
13. (nsc 301739 OR 65271 80 9) AND prostate
14. (70476 82 3 OR l01db07 OR novantrone) AND prostate

Current Controlled Trials (Internet - http://controlled-trials.com/)
Searched on 11th April 2005

Limits:

- No limits were applied
- All registers were searched

Strategy for Docetaxel
This search retrieved 25 references.

1. (docetaxel OR asodecel OR doxetal) AND prostate

2. (doxmil OR neocel OR plustaxano) AND prostate
3. (texot OR trazoteva OR trixotene) AND prostate
4. (dolectran OR donataxel) AND prostate
5. (daxotel OR taxotere) AND prostate
6. (NSC-628503 OR RP-56976) AND prostate
7. (114977-28-5 OR L01cd02) AND prostate

Strategy for Mitoxantrone
This search retrieved 58 references.

1. (mitozantrone OR mitoxantrone OR novantrone) AND prostate
2. (onkotrone OR batinel OR micraleve) AND prostate
3. (mitoxgen OR mitoxmar OR novatron) AND prostate
4. (misostol OR mitoxal OR neotalem) AND prostate
5. (genefadrone OR formyxan OR mitroxone) AND prostate
6. (serotron OR pralifan OR "cl 232315") AND prostate
7. (dihydroxyanthracenedione) AND prostate
8. (dhad OR "hidrocloruro de mitoxantrona") AND prostate
9. ("mitoxantroni hydrochloridum") AND prostate
10. ("mitrozantrone hydrochloride") AND prostate

CinicalTrials.gov (Internet - http://clinicaltrials.gov/)
Searched on 11th April 2005

Limits:
- No limits were applied

Strategy for Docetaxel
This search retrieved 55 references.

1. (docetaxel OR asodecel OR dolectran OR donataxel OR doxetal OR doxmil OR neocel OR plustaxano OR texot OR trazoteva OR trixotene OR daxotel OR taxotere) and prostate
2. (NSC-628503 OR RP-56976) AND prostate
3. (114977-28-5 OR L01cd02) AND prostate

Strategy for Mitoxantrone
This search retrieved 16 references.

1. (mitozantrone OR mitoxantrone OR novantrone) AND prostate
2. ("bp 2003" OR "usp 27" OR onkotrone OR batinel OR micraleve) AND prostate
3. (mitoxgen OR mitoxmar OR novatron) AND prostate
4. (misostol OR mitoxal OR neotalem) AND prostate
5. (genefadrone OR formyxan OR mitroxone) AND prostate
6. (serotron OR pralifan OR "cl 232315") AND prostate
7. (dihydroxyanthracenedione) AND prostate
8. (dhad OR "hidrocloruro de mitoxantrona") AND prostate
9. ("mitoxantroni hydrochloridum") AND prostate
10. ("mitrozantrone hydrochloride") AND prostate

11. ("nsc 301739" OR "65271 80 9") AND prostate
12. ("70476 82 3" OR "l01db07") AND prostate

10.1.2. Cost-effectiveness

MEDLINE and MEDLINE In Process And Other Non-Indexed Citations (Ovid Online – www.ovid.com)
1966 to May Week 4 2005 (MEDLINE) and June 02, 2005 (MEDLINE In Process)

Limits:

- No date limits were applied
- Animal-only studies were excluded
- No language limits were applied

This search retrieved 164 references from MEDLINE and 5 from MEDLINE In Process.

1. prostatic neoplasms/
2. ((prostate or prostatic) adj2 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or tumour$ or tumor$)).ti,ab.
3. 1 or 2
4. animal/ not (animal/ and human/)
5. 3 not 4
6. (utilit$ approach$ or health gain or hui or hui2 or hui 2 or hui3 or hui 3).ti,ab.
7. (health measurement$ scale$ or health measurement$ questionnaire$).ti,ab.
8. (standard gamble$ or categor$ scal$ or linear scal$ or linear analog$ or visual scal$ or magnitude estimat$).ti,ab.
9. (time trade off$ or rosser$ classif$ or rosser$ matrix or rosser$ distress$ or hrqol).ti,ab.
10. (index of wellbeing or quality of wellbeing or qwb).ti,ab.
11. (multiattribute$ health ind$ or multi attribute$ health ind$).ti,ab.
12. (health utilit$ index or health utilit$ indices).ti,ab.
13. (multiattribute$ theor$ or multi attribute$ theor$ or multiattribute$ analys$ or multi attribute$ analys$).ti,ab.
14. (health utilit$ scale$ or classification of illness state$ or 15 dimension).ti,ab.
15. health state$ utilit$.ti,ab.
16. well year$.ti,ab.
17. (multiattribute$ utilit$ or multi attribute$ utilit$).ti,ab.
18. health utilit$ scale$.ti,ab.
19. (euro qol or euro qual or eq-5d or eq5d or eq 5d or euroqol or euroqual).ti,ab.
20. (qualy or qaly or qualys or qalys or quality adjusted life year$).ti,ab.
21. willingness to pay.ti,ab.
22. (hye or hyes or health$ year$ equivalent$).ti,ab.
23. (person trade off$ or person tradeoff$ or time tradeoff$ or time trade off$).ti,ab.
24. theory utilit$.ti,ab.
25. (sf36 or sf 36).ti,ab.
26. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
27. (sf 6d or short from 6d).ti,ab.

28. or/6-27
29. 28 and 5
30. letter.pt.
31. editorial.pt.
32. comment.pt.
33. or/30-32
34. 29 not 33

EMBASE (OVID Online - http://www.ovid.com/)
1980 to 2005 week 22

Limits:

- No date limits were applied
- Animal-only studies were excluded
- No language limits were applied

This search retrieved 143 references.

1. Prostatic Intraepithelial Neoplasia/
2. ((prostate or prostatic) adj2 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or tumour$ or tumor$)).ti,ab.
3. 1 or 2
4. animal/ not (animal/ and human/)
5. 3 not 4
6. (utilit$ approach$ or health gain or hui or hui2 or hui 2 or hui3 or hui 3).ti,ab.
7. (health measurement$ scale$ or health measurement$ questionnaire$).ti,ab.
8. (standard gamble$ or categor$ scal$ or linear scal$ or linear analog$ or visual scal$ or magnitude estimat$).ti,ab.
9. (time trade off$ or rosser$ classif$ or rosser$ matrix or rosser$ distress$ or hrqol).ti,ab.
10. (index of wellbeing or quality of wellbeing or qwb).ti,ab.
11. (multiattribute$ health ind$ or multi attribute$ health ind$).ti,ab.
12. (health utilit$ index or health utilit$ indices).ti,ab.
13. (multiattribute$ theor$ or multi attribute$ theor$ or multiattribute$ analys$ or multi attribute$ analys$).ti,ab.
14. (health utilit$ scale$ or classification of illness state$ or 15 dimension).ti,ab.
15. health state$ utilit$.ti,ab.
16. well year$.ti,ab.
17. (multiattribute$ utilit$ or multi attribute$ utilit$).ti,ab.
18. health utilit$ scale$.ti,ab.
19. (euro qol or euro qual or eq-5d or eq5d or eq 5d or euroqol or euroqual).ti,ab.
20. (qualy or qaly or qualys or qalys or quality adjusted life year$).ti,ab.
21. willingness to pay.ti,ab.
22. (hye or hyes or health$ year$ equivalent$).ti,ab.
23. (person trade off$ or person tradeoff$ or time tradeoff$ or time trade off$).ti,ab.
24. theory utilit$.ti,ab.
25. (sf36 or sf 36).ti,ab.
26. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.

27. (sf 6d or short from 6d).ti,ab.
28. or/6-27
29. 28 and 5
30. letter.pt.
31. editorial.pt.
32. comment.pt.
33. or/30-32
34. 29 not 33

Cumulative Index to Nursing & Allied Health Literature (CINAHL) (Ovid Online – www.ovid.com)
1982 to May Week 4 2005

Limits:

- No date limits were applied
- No language limits were applied

This search retrieved 21 references.

1. prostatic neoplasms/
2. ((prostate or prostatic) adj2 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or tumour$ or tumor$)).ti,ab.
3. 1 or 2
4. (utilit$ approach$ or health gain or hui or hui2 or hui 2 or hui3 or hui 3).ti,ab.
5. (health measurement$ scale$ or health measurement$ questionnaire$).ti,ab.
6. (standard gamble$ or categor$ scal$ or linear scal$ or linear analog$ or visual scal$ or magnitude estimat$).ti,ab.
7. (time trade off$ or rosser$ classif$ or rosser$ matrix or rosser$ distress$ or hrqol).ti,ab.
8. (index of wellbeing or quality of wellbeing or qwb).ti,ab.
9. (multiattribute$ health ind$ or multi attribute$ health ind$).ti,ab.
10. (health utilit$ index or health utilit$ indices).ti,ab.
11. (multiattribute$ theor$ or multi attribute$ theor$ or multiattribute$ analys$ or multi attribute$ analys$).ti,ab.
12. (health utilit$ scale$ or classification of illness state$ or 15 dimension).ti,ab.
13. health state$ utilit$.ti,ab.
14. well year$.ti,ab.
15. (multiattribute$ utilit$ or multi attribute$ utilit$).ti,ab.
16. health utilit$ scale$.ti,ab.
17. (euro qol or euro qual or eq-5d or eq5d or eq 5d or euroqol or euroqual).ti,ab.
18. (qualy or qaly or qualys or qalys or quality adjusted life year$).ti,ab.
19. willingness to pay.ti,ab.
20. (hye or hyes or health$ year$ equivalent$).ti,ab.
21. (person trade off$ or person tradeoff$ or time tradeoff$ or time trade off$).ti,ab.
22. theory utilit$.ti,ab.
23. (sf36 or sf 36).ti,ab.
24. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
25. (sf 6d or short from 6d).ti,ab.

26. or/4-25
27. 3 and 26
28. letter.pt.
29. editorial.pt.
30. comment.pt.
31. or/28-30
32. 27 not 31

NHS Economic Evaluation Database (CRD administration database)
Searched: 6th June 2005

Limits:

- No date limits were applied
- No study design limits or language limits were applied

This search retrieved 22 references.

1. prostate(2w)neoplasm$
2. prostate(2w)cancer$
3. prostate(2w)carcinoma$
4. prostate(2w)adenocarcinoma$
5. prostate(2w)tumour$
6. prostate(2w)tumor$
7. prostatic(2w)neoplasm$
8. prostatic(2w)cancer$
9. prostatic(2w)carcinoma$
10. prostatic(2w)adenocarcinoma$
11. prostatic(2w)tumour$
12. prostatic(2w)tumor$
13. s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12
14. utilit$(w)approach$ or health(w)gain or hui or hui2 or hui(w)2 or hui3 or hui(w)3
15. health(w)measurement$(w)scale$ or health(w)measurement$(w)questionnaire$
16. standard(w)gamble$ or categor$(w)scal$ or linear(w)scal$ or linear(w)analog$ or visual(w)scal$ or magnitude(w)estimat$
17. time(w)trade(w)off$ or rosser$(w)classif$ or rosser$(w)matrix or rosser$(w)distress$ or hrqol
18. index(w2)wellbeing or quality(w2)wellbeing or qwb
19. multiattribute$(w)health(w)ind$ or multi(w)attribute$(w)health(w)ind$
20. health(w)utilit$(w)index or health(w)utilit$(w)indices
21. multiattribute$(w)theor$ or multi(w)attribute$(w)theor$ or multiattribute$(w)analys$ or multi(w)attribute$(w)analys$
22. health(w)utilit$(w)scale$ or classification(w2)illness(w)state$ or 15(w)dimension
23. health(w)state$(w)utilit$
24. well(w)year$
25. multiattribute$(w)utilit$ or multi(w)attribute$(w)utilit$
26. health(w)utilit$(w)scale$
27. euro(w)qol or euro(w)qual or eq-5d or eq5d or eq(w)5d or euroqol or euroqual
28. qualy or qaly or qualys or qalys or quality(w)adjusted(w)life(w)year$

29. willingness(w)to(w)pay
30. hye or hyes or health$(w)year$(w)equivalent$
31. person(w)trade(w)off$ or person(w)tradeoff$ or time(w)tradeoff$ or time(w)trade(w)off$
32. theory(w)utilit$
33. sf36 or sf(w)36
34. short(w)form(w)36 or shortform(w)36 or sf(w)thirtysix or sf(w)thirty(w)six or shortform(w)thirtysix or shortform(w)thirty(w)six or short(w)form(w)thirtysix or short(w)form(w)thirty(w)six
35. sf(w)6d or short(w)from(w)6d
36. s14 or s15 or s16 or s17 or s18 or s19 or s20 or s21 or s22 or s23 or s24 or s25 or s26 or s27 or s28 or s29 or s30 or s31 or s32 or s33 or s34
37. s36 and s13

Appendix 10.2. Excluded studies

Study details	Reason for exclusion
Ahmad (2004)[90]	Commentary/overview
Anonymous (1999)[91]	Not an RCT
Anonymous (1999)[91]	Not an RCT
Anonymous (2000)[92]	No prednisone/prednisolone (not licensed)
Anonymous (2002)[93]	No prednisone/prednisolone (not licensed)
Anonymous (2002)[94]	Not an RCT
Anonymous (2002)[95]	Not an RCT
Anonymous (2002)[96]	Wrong patient group
Anonymous (2004)[97]	Commentary/overview
Anonymous (2004)[98]	No prednisone/prednisolone (not licensed)
Anonymous (2004)[99]	No prednisone/prednisolone (not licensed)
Anonymous (2004)[100]	Not an RCT
Anonymous (2004)[101]	No prednisone/prednisolone (not licensed)
Anonymous (2004)[102]	Not an RCT
Anonymous (2004)[103]	Not an RCT
Anonymous (2004)[104]	Not an RCT
Anonymous (2004)[105]	Not an RCT
Anonymous (2004)[106]	Not an RCT
Anonymous (2004)[107]	Wrong intervention drug combination
Anonymous (2005)[108]	Wrong patient group
Anonymous (2005)[109]	Wrong patient group
Anonymous (2005)[110]	Wrong patient group
Anonymous (2005)[111]	Wrong patient group
Anonymous (2000)[112]	Duplicate report
Anonymous (2002)[113]	Not an RCT
Anonymous (2002)[114]	Not an RCT
Anonymous (2004)[115]	Wrong patient group
Anonymous (2005)[116]	Not an RCT
Anonymous (2005)[117]	Wrong intervention drug combination
Anonymous (2001)[118]	Background
Anonymous (2000)[119]	Background
Arcenas (2003)[120]	Not an RCT
Arlen (2002)[121]	Commentary/overview
Autorino (2003)[122]	Commentary/overview
Aventis Pharma (2004)[123]	Background
Aventis Pharma (2004)[124]	Background
Aventis Pharma (2004)[125]	Background
Aventis Pharma (2004)[16]	Background
Beedassy (1999)[126]	Commentary/overview
Beer[127]	Not an RCT

Beer (2003)[128]	Background
Beer (2002)[129]	Background
Beer (2004)[130]	Background
Beer (2001)[131]	Background
Beitz (1999)[132]	Commentary/overview
Bernardi (2004)[133]	Not an RCT
Berry (2003)[134]	Not an RCT
Bloomfield (1997)[135]	Not an RCT
Bloomfield (1997)[136]	Not an RCT
Bosnjak (2003)[137]	Background
Bracarda (2002)[138]	Not an RCT
Brandes[139]	Not an RCT
Bucher (1997)[63]	Background
Cancer Research UK (2004)[1]	Background
Cancer Research UK (2004)[2]	Background
Cancer Research UK (2004)[140]	Background
Canil (2004)[141]	Commentary/overview
Carducci (1999)[142]	Commentary/overview
Centre for Reviews and Dissemination (2001)[23]	Background
Chamberlain (1997)[11]	Background
Chang (2005)[143]	Background
Chatta (2004)[144]	Commentary/overview
Clarke (2004)[145]	Background
Coleman (2004)[10]	Background
Collette (2004)[146]	Commentary/overview
Copur (2001)[147]	Not an RCT
Crawford (2000)[148]	Commentary/overview
Crawford (2002)[149]	Wrong patient group
Culine (2000)[150]	Commentary/overview
Culine (2000)[151]	Commentary/overview
Dahut (2004)[152]	No prednisone/prednisolone (not licensed)
D'Amico (2004)[153]	Not an RCT
De Mulder (2002)[154]	Background
De Wit (2005)[155]	Commentary/overview
DeGrendele (2003)[156]	Commentary/overview
Denes (1997)[157]	Background
Department of Health[4]	Background
Deutsch (2004)[7]	Background
Diaz (2004)[158]	Commentary/overview
Dogliotti (2003)[159]	Commentary/overview
Dowling (2000)[160]	Background
Drummond (1997)[24]	Background
Efficace (2003)[161]	Wrong patient group
Eisenberger (1998)[12]	Background
Esper (1997)[84]	Commentary/overview

Eymard (2004)[162]	Duplicate
Fakih (2002)[163]	Background
Ferrero (2004)[164]	Background
Ferrero (2003)[165]	Not an RCT
Fichtner (2000)[166]	Commentary/overview
Font (2005)[167]	Not an RCT
Fossa (2001)[168]	Background
Freeman (2003)[169]	Not an RCT
Friedland (1999)[170]	Not an RCT
Gaffar (2003)[171]	Not an RCT
Garcia-Altes (2001)[172]	Background
Gilligan (2002)[173]	Not an RCT
Goodin (2003)[174]	Wrong patient group
Gravis[175]	Not an RCT
Gravis (2003)[176]	Background
Gravis (2002)[177]	Not an RCT
Gronberg (2003)[5]	Background
Guimaraes (2002)[178]	Not an RCT
Gustafson (2003)[179]	Commentary/overview
Hainsworth (2004)[180]	Background
Halabi (2003)[181]	Not an RCT
Heidenreich (2004)[182]	Background
Heidenreich (2003)[183]	Not an RCT
Heidenreich[184]	Not an RCT
Heidenreich[185]	Not an RCT
Heidenreich (2003)[186]	Not an RCT
Heidenreich (2003)[187]	Not an RCT
Hennequin (2004)[188]	Commentary/overview
Higano (2004)[189]	Not an RCT
Higano (2004)[190]	Not an RCT
Hussain (1999)[191]	Background
Joint Formulary Committee (2005)[18]	Background
Joly (2004)[192]	Background
Karavasilis (2003)[193]	Not an RCT
Kasamon (2004)[194]	Commentary/overview
Khalaf (2002)[195]	Not an RCT
Khan (2003)[196]	Background
Kish (2001)[197]	Commentary/overview
Knox (2001)[198]	Commentary/overview
Ko (2001)[199]	Wrong intervention drug combination
Kolodziej[200]	Not an RCT
Kornbloth (2001)[201]	Not an RCT
Kosty[202]	Not an RCT
Kozloff[203]	Not an RCT
Kozloff[204]	Not an RCT
Kuebler (2003)[205]	Not an RCT
Laber[206]	Not an RCT

Laber (2003)[207]	Not an RCT
Lara (2004)[208]	No prednisone/prednisolone (not licensed)
Loblaw (2004)[209]	Wrong patient group
Logothetis (2002)[210]	Commentary/overview
Lubiniecki (2004)[211]	Background
Martel (2003)[212]	Commentary/overview
Mattioli (1998)[213]	Not an RCT
Medline Plus (2005)[214]	Background
Miller (2002)[215]	Not an RCT
Miller (2003)[216]	Not an RCT
Montero (2005)[217]	Background
Moore (1994)[218]	Not an RCT
Muthuramalingam (2004)[9]	Background
Nabhan (2005)[219]	Background
National Cancer Institute[220]	Wrong patient group
National Cancer Institute[221]	Not an RCT
National Cancer Institute[222]	Not an RCT
National Cancer Institute[223]	Not an RCT
National Horizon Scanning Centre (2003)[19]	Background
National Institute for Clinical Excellence (2002)[8]	Background
Newling (1999)[224]	Commentary/overview
Office for National Statistics (2002)[3]	Background
Oh (2000)[225]	Commentary/overview
Oh (1998)[226]	Commentary/overview
Olson (2000)[227]	Commentary/overview
Parmar (1998)[25]	Background
Parvez (2003)[228]	Commentary/overview
Petrioli (2003)[229]	Not an RCT
Petrylak (1999)[230]	Commentary/overview
Petrylak (2000)[231]	Commentary/overview
Petrylak (2000)[232]	Not an RCT
Petrylak (2002)[13]	Background
Petrylak (2002)[233]	Commentary/overview
Picus (1999)[234]	Commentary/overview
Picus (1999)[235]	Not an RCT
Pozzessere (2002)[236]	Not an RCT
Price (2004)[237]	Commentary/overview
Raghavan[238]	Not an RCT
Rago (2003)[239]	Not an RCT
Rajasenan[240]	Not an RCT
Rexer (2004)[241]	Commentary/overview
Rosenberg[242]	Wrong patient group
Rosenberg[243]	Wrong patient group
Rosenthal (2000)[244]	Commentary/overview

Ruchlin (2001)[245]	Background
Salimichokami (2003)[246]	No prednisone/prednisolone (not licensed)
Samelis (2000)[247]	Not an RCT
Sanofi-aventis (2005)[61]	Background
Sartor (2002)[68]	Commentary/overview
Sava (2005)[248]	Background
Scher (1995)[249]	Commentary/overview
Scholz[250]	Not an RCT
Schwartz[251]	Not an RCT
Shaneyfelt (2000)[6]	Background
Sheen (2004)[252]	Not an RCT
Sherman (2001)[253]	Background
Small (1999)[254]	Commentary/overview
Smith (1999)[255]	Commentary/overview
Song (2003)[62]	Background
Stein (1999)[15]	Background
Stein[256]	Not an RCT
Syed (2003)[257]	Commentary/overview
Tannock (2001)[258]	Commentary/overview
Tay (2004)[259]	Not an RCT
Trump (2003)[260]	Not an RCT
Tyagi (2003)[261]	Commentary/overview
US Food and DRug Administration (2004)[262]	Background
Vaishampayan (1999)[14]	Background
Valerio (2003)[263]	Not an RCT
Van Poppel (2005)[264]	Background
Vogelzang (1996)[265]	Commentary/overview
Vogelzang (1999)[266]	Commentary/overview
Vogelzang (2001)[267]	Commentary/overview
Vogelzang (1998)[268]	Commentary/overview
Vollmer (2002)[269]	Not an RCT
Walczak (2003)[270]	No prednisone/prednisolone (not licensed)
Walsh (2005)[271]	Commentary/overview
Wang[272]	Wrong patient group
Wang (2001)[273]	Commentary/overview
Warren G Magnuson Clinical Center[274]	Not an RCT
Weitzman (2000)[275]	Background
Willan (2001)[276]	Background
Willan (2001)[277]	Background
Willan (2001)[278]	Background
Wiseman (1997)[279]	Background
Wolf (2003)[280]	Wrong patient group
Wolff (2003)[281]	Commentary/overview
Zivin (2001)[282]	Background

Appendix 10.3. Trials only available in abstract form

Meeting: 2004 ASCO Annual Meeting
Category: Genitourinary Cancer
SubCategory: Prostate Cancer

Phase II randomized trial of docetaxel plus estramustine (DE) versus docetaxel (D) in patients (pts) with hormone-refractory prostate cancer (HRPC): A final report

Abstract No: 4603
Citation: *Journal of Clinical Oncology*, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 22, No 14S (July 15 Supplement), 2004

Authors: J.-C. Eymard, F. Joly, F. Priou, A. Zannetti, A. Ravaud, P. Kerbrat, M. Mousseau, B. Paule, F. Touze, E. Ecstein-Fraisse; Institut Jean Godinot, Reims, France; Centre Jean François Baclesse, Caen, France; Centre Hospitalier Départemental, La Roche/Yon, France; Clinique du Parc, Cholet, France; Institut Bergonié, Bordeaux, France; Centre Eugène Marquis, Rennes, France; CHU Michallon, Grenoble, France; Hospital Henri Mondor, Créteil, France; Laboratoire Aventis, Paris, France

The study evaluated docetaxel in combination with estramustine versus docetaxel alone in patients with hormone-refractory prostate cancer (HRPC). To be eligible for the study patients had to have WHO performance status ≤ 2, appropriate renal, hepatic, and hematologic function, no prior chemotherapy and withdrawal of antiandrogen therapy. Patients received docetaxel (70 mg/m^2 IV over one hour on day one every three weeks) plus estramustine (560 mg per day orally starting one day prior to docetaxel infusion, for 5 consecutive days) or docetaxel alone (75 mg/m^2 IV over one hour on day one every three weeks) for a maximum of 6 cycles. Prophylactic warfarin (1 mg/d orally) was given continuously in the docetaxel plus estramustine group. Corticosteroid was given before and after docetaxel infusion in both groups. Outcomes of interest were PSA decline, safety and quality of life.

92 patients were randomized, but 1 patient did not receive treatment. Median age was 68 years (range: 46–86), performance status 0/1/2 (32/50/9 patients), median PSA was 115 ng/ml (range: 0.3–1585), and 40 patients (22 in the docetaxel plus estramustine group and 18 in the docetaxel alone group) had measurable disease. With a median number of 6 treatment cycles in both arms, cycle delays >7 days were more frequent in the docetaxel plus estramustine group (15% patients) than the docetaxel alone group (11% pts); dose reduction was similar, 4.3% versus 4.5% patients, respectively. Median follow-up was 12.8 months.

Response in the docetaxel plus estramustine group versus the docetaxel group, respectively, was: PSA decline >50%: 68% versus 29%; PSA decline >75%: 36% versus 16%; median PSA response duration was 6 months in both groups. Of 40 patients with measurable disease, PR was observed in 18.2% (docetaxel plus estramustine group) versus 16.7% (docetaxel alone group). Median time to progression in the docetaxel plus estramustine group was 5.7 months (range: 4.7–5.8) versus 2.8 (range: 2–6.9) in the docetaxel alone group.

The main grade 3–4 hematologic toxicities among patients in the docetaxel plus estramustine group versus the docetaxel alone group, respectively, were neutropenia 25.5% versus 27.3% and anaemia 10.6% versus 2.3%. The main grade 3−4 treatment toxicities were: thrombophlebitis (1 patient in the docetaxel plus estramustine group), allergic reaction (1 patient in the docetaxel plus estramustine group), febrile neutropenia (1 patient in each group) and fatal acute pulmonary edema (1 patient in the docetaxel alone group).

There was no worsening in quality of life using the FACT-P instrument and the pain score was stable throughout treatment in both groups.

Conclusion: Docetaxel-based regimens are active in hormone-refractory prostate cancer with predictable and manageable toxicity profiles.

Meeting: 39th Annual Meeting of the American Society of Clinical Oncology
Category: Genitourinary Cancer

Combining angiogenesis inhibitors with cytotoxic chemotherapy enhances PSA response in hormone-refractory prostate cancer (HRPC), a randomized study of weekly docetaxel alone or in combination with thalidomide

Abstract No: 1725

Authors: M. Salimichokami; Mehr Medical Center, Tehran, Iran

The study evaluated docetaxel in combination with thalidomide versus docetaxel alone in patients with hormone-refractory prostate cancer (HRPC). Patients received docetaxel (35 mg/m^2 IV weekly for 6 consecutive weeks followed by 2 weeks rest) plus thalidomide (100 mg per day orally) or docetaxel alone (35 mg/m^2 IV weekly for 6 consecutive weeks followed by 2 weeks rest). All patients in both groups received prophylactic ASA (200 mg/day throughout the study) to prevent thrombotic episodes.

Accrual started in Oct. 2001 and is ongoing. To date 55 patients have been accrued using standard phase-2 eligibility criteria. All patients were chemo-naive but no one was excluded based on any type of hormone/radiation/radioisotope treatment. Median age was 65 and all patients had ECOG performance status 0-1.

Using the generally accepted consensus criteria 20 (66%) of 30 patients in the combination arm showed PSA decline of 50% or more compared with 8 (32%) of 25 patients receiving docetaxel alone.

A total of 660 weekly docetaxel infusions were administered. Severe marrow toxicity was quite rare. Grade 2 or more neutropenia was seen only in 5 patients. Grade 2 or more thrombocytopenia was also infrequent and was shown in 3 patients. Two patients in our combination arm developed D.V.T. which cleared shortly after anticoagulant therapy started.

Our study supports the previous preclinical and clinical evidence suggesting the synergistic effect of combining an antiangiogenic agent with a cytotoxic drug in the treatment of human prostate cancer.

Appendix 10.4. Quality assessment strategy

A. Studies of clinical effectiveness were assessed using the following criteria, based on CRD Report No. 4[23]

1. Was the method used to assign participants to the treatment groups really random? *(Computer generated random numbers and random number tables will be accepted as adequate, while inadequate approaches will include the use of alternation, case record numbers, birth dates and days of the week)*
2. Was the allocation of treatment concealed? *(Concealment will be deemed adequate where randomisation is centralised or pharmacy-controlled, or where the following are used: serially-numbered identical containers, on-site computer based systems where the randomisation sequence is unreadable until after allocation, other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque).*
3. Was the number of participants who were randomised stated?
4. Were details of baseline comparability presented?
5. Was baseline comparability achieved?
6. Were the eligibility criteria for study entry specified?
7. Were any co-interventions identified that may influence the outcomes for each group?
8. Were the outcome assessors blinded to the treatment allocation?
9. Were the individuals who administered the intervention blinded to the treatment allocation?
10. Were the participants who received the intervention blinded to the treatment allocation?
11. Was the success of the blinding procedure assessed?
12. Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?
13. Were the reasons for withdrawals stated?
14. Was an intention to treat analysis included?

Items were graded in terms of yes (item properly addressed), no (item not properly addressed), partially (item partially addressed), unclear or not enough information, or not applicable.

B. Studies of cost-effectiveness were assessed using the following criteria, which is an updated version of the checklist developed by Drummond[24]

Study question

1. Costs and effects examined
2. Alternatives compared
3. The viewpoint(s)/perspective of the analysis is clearly stated *(e.g. NHS, society)*

Selection of alternatives

4. All relevant alternatives are compared *(including do-nothing if applicable)*
5 The alternatives being compared are clearly described *(who did what, to whom, where and how often)*
6. The rationale for choosing the alternative programmes or interventions compared is stated

Form of evaluation

7. The choice of form of economic evaluation is justified in relation to the questions addressed.
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?

Effectiveness data

9. The source(s) of effectiveness estimates used are stated *(e.g. single study, selection of studies, systematic review, expert opinion)*
10. Effectiveness data from RCT or review of RCTs
11. Potential biases identified (especially if data not from RCTs)
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)

Costs

13. All the important and relevant resource use included
14. All the important and relevant resource use measured accurately (with methodology)
15. Appropriate unit costs estimated (with methodology)
16. Unit costs reported separately from resource use data
17. Productivity costs treated separately from other costs
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.

Benefit measurement and valuation

19. The primary outcome measure(s) for the economic evaluation are clearly stated *(cases detected, life years, QALYs, etc.)*
20. Methods to value health states and other benefits are stated (e.g. *time trade off*)
21. Details of the individuals from whom valuations were obtained are given *(patients, members of the public, health care professionals etc.)*

Decision modelling

22. Details of any decision model used are given (e.g. *decision tree, Markov model*)

23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified
24. All model outputs described adequately.

Discounting

25. Discount rate used for both costs and benefits
26. Do discount rates accord with NHS guidance (1.5%-2% for benefits; 6% for costs)?

Allowance for uncertainty

Stochastic analysis of patient-level data

27. Details of statistical tests and confidence intervals are given for stochastic data
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves).
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).

Stochastic analysis of decision models

30. Are all appropriate input parameters included with uncertainty?
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?
32. Are the probability distributions adequately detailed and appropriate?
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).

Deterministic analysis

34. The approach to sensitivity analysis is given (*e.g. univariate, threshold analysis etc*)
35. The choice of variables for sensitivity analysis is justified
36. The ranges over which the variables are varied are stated

Presentation of results

37. Incremental analysis is reported using appropriate decision rules
38. Major outcomes are presented in a disaggregated as well as aggregated form
39. Applicable to the NHS setting

Items were graded in terms of yes (item properly addressed), no (item not properly addressed), unclear or not enough information, not applicable or not stated.

Appendix 10.5. Calculation of hazard ratios

Using the method outlined by Parmar et al.[25] we undertook the estimation of hazard ratios and corresponding 95% confidence intervals if such data were not reported in the trial publications identified. If the hazard ratio is not reported, it can be computed directly if the observed and expected numbers are presented for both treatment groups. However, this information is rarely reported. The next preferred method is estimating the hazard ratio from the quoted p-value and number of observed events in the trial (an example of which is shown below). The final option is estimating the hazard ratio and confidence intervals directly from the survival curve.

Survival curves are fairly commonly reported, however this method is prone to further challenges. In order to estimate the hazard ratio in this way, a general approach is to split the time axis into T non-overlapping time intervals. Then using the probabilities of survival for each group estimated from the survival curve, the hazard ratios for each time interval are calculated. These are then combined in a stratified way across time intervals to obtain an overall hazard ratio for the trial. This technique has its challenges including being time consuming and problems can arise when attempting to read survival probabilities from poorly drawn curves, meaning that duplicate data extraction from the survival curve is of paramount importance.

Example using p-values and observed numbers of events.

In order to estimate the hazard ratio and its corresponding 95% confidence intervals we need to extract the p-value (the log-rank and Mantel-Haenszel statistics are considered to be equivalent here) and the total number of observed events, which will be known as p and O respectively. The process of calculating the hazard ratio and its 95% confidence intervals is iterative, consisting of six steps as follows:

Step 1: Calculate V

$$V = O / 4$$

Step 2: Calculate $O_r - E_r$

$$(O_r - E_r) = ½ \times \sqrt{O} \times \Phi^{-1}(1-p/2)$$

Step 3: Calculate the log hazard ratio, ln(HR), using the answers from Steps 1 and 2.

$$\ln(HR) = (O_r - E_r) / V$$

Step 4: Calculate the hazard ratio, HR

$$HR = \exp(\ln(HR))$$

Step 5: Calculate the variance of the log hazard ratio, Var[ln(HR)]

$$Var[\ln(HR)] = 1/V$$

Step 6: Calculate the 95% confidence interval for HR

$$95\%\ CI = \exp [\ln(HR) \pm 1.96 \times \sqrt{var[\ln(HR)]}]$$

Worked Example – CALGB 9182 Overall survival

In this example, an unadjusted p-value of 0.77 (p) is presented with a total of 58 deaths in the mitoxantrone group and 68 deaths in the hydrocortisone group at the time of analysis. This gives a total number of observed events of 58+68 = 126 (O). Working through the steps as outlined above, we have:

Step 1: Calculate V

$$V = O / 4$$
$$V = 126/4 = 31.5$$

Step 2: Calculate $O_r - E_r$

$$(O_r - E_r) = ½ \times \sqrt{126} \times \Phi^{-1}(1-0.77/2)$$
$$(O_r - E_r) = 1/2 \times 11.22 \times 0.2923 = 1.64095$$

Step 3: Calculate the log hazard ratio, ln(HR), using the answers from Steps 1 and 2.

$$\ln(HR) = (O_r - E_r) / V$$
$$\ln(HR) = 1.64095/31.5 = 0.052094$$

Step 4: Calculate the hazard ratio, HR

$$HR = \exp(\ln(HR))$$
$$HR = \exp(0.052094) = 1.053474$$

Step 5: Calculate the variance of the log hazard ratio, Var[ln(HR)]

$$Var[\ln(HR)] = 1/V$$
$$Var[\ln(HR)] = 1/31.5 = 0.0317$$

Step 6: Calculate the 95% confidence interval for HR

$$95\%\ CI = \exp\ [\ln(HR) \pm 1.96 \times \sqrt{var[\ln(HR)]}]$$
$$95\%\ CI = \exp[0.052094 \pm 1.96 \times \sqrt{0.0317}]]$$
$$95\%\ CI = 0.747, 1.494$$

Therefore the hazard ratio for death in this example is 1.05 (95% CI : 0.747, 1.494).

Appendix 10.6. Data extraction tables

Study Details and Design	Participant Details	Intervention Details	Results	Conclusion and Comments
Author: Tannock 2004[27] **Country:** 24 countries, including Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Finland, France, Germany, Hungary, Italy, Lebanon, the Netherlands, Poland, Russia, Slovak Republic, South Africa, Spain, Sweden, United Kingdom, United States. **Primary source:** Hand searching **Aim:** To determine whether docetaxel plus prednisone improves overall survival compared to mitoxantrone plus prednisone in men with advanced, hormone-refractory prostate cancer. **Trial ID:** TAX 327 **Phase:** Phase III **Length of follow-up:** (Median) I (1): 20.8 months; I (2): 20.7 months; C: 20.7 months **Number and times of follow-up measurements:** Physical examinations and blood tests: every 3 weeks. Imaging studies: intervals of 6 to 9 weeks and repeated	**Number randomised:** 1,006 men **Disease characteristics:** Gleason Score: I(1): ≤7=42%; 8-10=31%; unavailable= 26%. I(2): ≤7=40%; 8-10=31%; unavailable= 29%. C: ≤7=42%; 8-10=28%; unavailable= 30%. Karnofsky performance-status score (60%-70%): I(1):13%; I(2):12%; C: 14% PSA (ng/ml), Median, (≥20 ng/ml, %): I(1):114 (87); I(2):108 (84); C:123 (89) Pain present (PPI score ≥2 or analgesic score of ≥10): I(1): 45%; I(2): 45%; C: 46% Evidence of progression at entry: Bone scan: I(1): 71%; I(2): 69%; C: 69% Increase in measurable lesions: I(1): 28%; I(2): 30%; C: 28% Increase in non-measurable lesions: I(1): 13%; I(2): 16%; C: 15% Increased PSA: I(1): 72%; I(2): 66%; C: 68% **Previous treatments:** Prostatectomy: I(1): 19%; I(2): 24%; C: 21% Radiotherapy (<25% bone marrow): I(1): 52%; I(2): 44%; C: 51% Estramustine: I(1): 19%; I(2): 18%; C: 20%	**Intervention 1:** 75 mg docetaxel per m^2 i.v. (for 1 hour) on day 1 every 21 days + 5 mg prednisone (or prednisolone, if prednisone unavailable) orally twice daily from day 1+8 mg dexamethasone given 12 hours, 3 hours and 1 hour before docetaxel infusion. Up to 10 cycles of treatment were planned, and treatment delays of up to 2 weeks and up to 2 dose reductions were allowed. Dose reductions were required in the presence of grade 4 neutropenia for at least 7 days, an infection, or grade 3-4 neutropenia with an oral temperature ≥38.5 °C. Dose reduction or treatment delay was also stipulated for patients with an absolute neutrophil count of <1500/mm^3 on a treatment day, or in the presence of grade 3-4 thrombocytopenia. **No. randomised:** 335 **Route of administration:** Docetaxel: i.v.; prednisone: p.o. **Dose:** 75 mg doctaxel +5 mg prednisone. **No. of cycles:** Up to 10 cycles. **Length per cycle:** 21 days. **Intervention 2:** 30 mg docetaxel per m^2 i.v. (for 30 mins) on days	**Outcome 1: Overall survival** Time from the date of randomisation to the date of death from any cause or censored at the date of last contact. Median Survival: (N=1006) I(1): 18.9 months (95% CI: 17.0-21.2) I(2): 17.4 months (95% CI: 15.7-19.0) C: 16.5 months (95% CI: 14.4-18.6) From Eisenberger et al. (2004) [36]: I(1)+ I(2): 18.3 months HR for death: I(1)vs C: 0.76 (95% CI:0.62-0.94, P=0.009) I(2) vs C: 0.91 (95% CI: 0.75-1.11. P=0.36) [I(1)+I(2) vs C: 0.83 (95% CI: 0.70-0.99, P=0.04)] The analysis was planned after 535 deaths had occurred: I(1): 166/335 (50%) died. I(2): 190/334 (57%) died. C: 201/337 (60%) died. HRs adjusted using a backward selection model, eliminating non-significant factors at P<0.10, comprising: age (<65vs ≥65), visceral involvement (yes vs no), liver involvement (yes vs no), number of prior hormonal manipulations (≤2 vs >2), prior estramustine (yes vs no), presence of rising PSA alone vs presence of other indications of progression, baseline haemoglobin level, baseline serum level of alkaline phosphotase. Visceral involvement, high baseline alkaline phosphatase level and a low haemoglobin level were negative prognostic factors, whereas a rising serum PSA level as the sole indicator of progression was a favourable factor. The survival benefit of I(1) was consistent across subgroups defined according to the presence or absence of pain at baseline, the Karnofsky performance-status score and age (data not shown).	**Authors' conclusions:** When given with prednisone, treatment with docetaxel every three weeks led to superior survival and improved rates of response in terms of pain, serum PSA level, and quality of life, as compared with mitoxantrone plus prednisone. **Comments:** The study was supported by Aventis, with consulting fees from Aventis received by most of the authors. Aventis also collected and maintained the data and undertook the statistical analysis, but the final content of the article was determined by the investigators.

after 4 weeks to confirm responses **Method of randomisation: -Assignment/allocation:** centralised, permuted-block allocation, stratified by baseline pain level (present: median PPI score ≥2 or mean analgesic score ≥10 vs absent: median PPI <2 and a mean analgesic score <10) and Karnofsky performance-status score (≤70% vs ≥80%). **ITT analysis performed:** Yes. Three comparisons of interest: weekly docetaxel compared to mitoxantrone, 3-weekly docetaxel compared to mitoxantrone and both docetaxel groups (combined) compared to mitoxantrone.(Bonferroni method used). **Per protocol analysis performed:** Not stated. **Comments:** **Baseline comparability:** Baseline characteristics were well-balanced among three treatment groups. **Eligibility criteria specified:** Yes **Co-interventions:** Premedication with dexamethasone was required	Hormonal manipulations: I(1):1=9%; 2=68%; >2=23% I(2):1=8%; 2=72%; >2=21% C:1=6%; 2=69%; >2=25% Prior treatment with corticosteroids was permitted. Four weeks must have elapsed since prior surgery or radiotherapy and enrolment. At least four weeks had to have elapsed since taking antiandrogens (six weeks for bicalutamide) and enrolment. **Median age of participants:** I(1): 68; I(2): 69; C: 68. **Age range of participants:** I(1): 42-92; I(2): 36-92; C: 43-86 **Other participant characteristics:** Extent of disease: Bone metastases: I(1): 90%; I(2): 91%; C: 92% Visceral disease: I(1): 22%; I(2): 24%; C: 22% Measurable lesions: I(1): 40%; I(2): 39%; C: 40% Race (from Dagher et al. (2004)[34] : Black: I(1): 2%; I(2): 2%; C: 3% Caucasian: I(1): 93%; I(2):93%; C: 93% Hispanic: I(1):2%; I(2):2%; C:3% Oriental: I(1):1%; I(2):1%; C:1% Other: I(1):1%; I(2):2%; C:1% Staging at diagnosis (from Dagher et al. (2004)[34] : Stage I:	1,8,15,22 and 29 in a 6-week cycle + 5 mg prednisone (or prednisolone, if prednisone unavailable) orally twice daily from day 1+8 mg dexamethasone given 1 hour before docetaxel infusion. Up to 5 cycles of treatment were planned, and treatment delays of up to 2 weeks and up to 2 dose reductions were allowed. Dose reductions were required in the presence of grade 4 neutropenia for at least 7 days, an infection, or grade 3-4 neutropenia with an oral temperature ≥38.5 °C. Dose reduction or treatment delay was also stipulated for patients with an absolute neutrophil count of <1000/mm^3 on a treatment day, or in the presence of grade 3-4 thrombocytopenia. **No. randomised:** 334 **Route of administration:** docetaxel :i.v.; prednisone: p.o. **Dose:** 30 mg docetaxel +5 mg prednisone **No. of cycles:** Up to 5. **Length per cycle:** 6 weeks. **Control:** 12 mg mitoxantrone per m^2 (for 30 mins) on day 1 every 21 days + 5 mg prednisone (or prednisolone, if prednisone unavailable) orally twice daily from day 1. Up to 10 cycles of treatment were planned, and treatment delays of up to 2 weeks and up to 2 dose reductions were	*From Industry Submission:* After 2 years, just <30% receiving C had survived and just <40% receiving I(1) had survived. Subgroup: overall survival according to further chemo (I(1) vs C). No further chemotherapy: I(1): n=156; C: n=171 HR=0.745 (95% CI: 0.554-1.001) Further chemotherapy: I(1): n=179; C: n=166 HR=0.815 (95% CI: 0.608-1.092) HR stratified for baseline pain and Karnofsky performance. **Outcome 2: Progression free survival** Not reported. **Outcome 3: Response rate** Tumour response: evaluated with use of World Health Organisation criteria. Number evaluated: (N=412) I(1): 141; I(2): 134; C: 137 Response rate: I(1):12% (95% CI:7-19, P=0.11) I(2): 8% (95% CI:4-14, P=0.59) C: 7% (95% CI:3-12) **Outcome 4: PSA decline** ≥50% reduction from baseline in PSA levels maintained for at least 3 weeks. Number evaluated: (N=873) I(1): 291; I(2): 282; C:300 Response rate: I(1):45% (95% CI:40-51, P<0.0001) I(2): 48% (95% CI:42-54, P=0.0005) C: 32% (95% CI:26-37)	

in the docetaxel groups. Antiemetic medication prescribed according to local practice. Treatment with granulocyte colony-stimulating factor was allowed for patients with febrile neutropenia. Systemic corticosteroids (other than dexamethasone and prednisone) and bisphosphonates were not permitted. Patients had to be receiving primary androgen-ablation therapy as maintenance therapy. **Blinding:** - **Outcome assessor:** No. - **Carer:** No. - **Patient:** No. - **Success assessed:** No. **80% Follow-up:** Yes.	I(1): 0%; I(2): 0%; C: 0% Stage II: I(1): 16%; I(2): 15%; C: 17% Stage III: I(1): 18%; I(2): 14%; C: 15% Stage IV: I(1): 57%; I(2): 58%; C: 54% Missing: I(1): 9%; I(2): 13%; C: 14% **Comments about participants:** **Inclusion/exclusion criteria:** Histologically or cytologically confirmed adenocarcinoma of the prostate and clinical or radiologic evidence of metastatic disease, with disease progression during hormonal therapy. Patients had to be receiving primary androgen-ablation therapy as maintenance therapy. Criteria for progressive disease were an increase in serum PSA level on three consecutive measurements obtained at least one week apart, or evidence from physical examination or imaging studies. Patients were ineligible if they received treatment with cytoxic agents (except estramustine), or radioisotopes. Normal cardiac function and a Karnofsky performance-status score of at least 60% were required, and patients were ineligible if they suffered from any other cancer (except basal or squamous-cell skin cancer) in the five years prior to enrolment. Patients with brain or leptomeningeal metastases, or symptomatic peripheral neuropathy of grade 2 or higher, or other serious medical condition, were also ineligible. Laboratory criteria for eligibility were a neutrophil count ≥1500/mm^3, haemoglobin ≥10.0g/dL, platelet count ≥100,000/mm^3, bilirubin level < upper	allowed. Dose reductions were required in the presence of grade 4 neutropenia for at least 7 days, an infection, or grade 3-4 neutropenia with an oral temperature ≥38.5 °C. Dose reduction or treatment delay was also stipulated for patients with an absolute neutrophil count of <1500/mm^3 on a treatment day, or in the presence of grade 3-4 thrombocytopenia. **No. randomised:** 337 **Route of administration:** Mitoxantrone: infusion; prednisone: p.o. **Dose:** 12 mg mitoxantrone +5 mg prednisone. **No. of cycles:** Up to 10 cycles. **Length per cycle:** 21 days. **Comments about intervention/control:** From Eisenberger et al. (2004) [36]: Planned treatment delivered: I(1): 98%; I(2): 96%; C: 99% From Centre for Drug Evaluation and Research (2004)[37]: Dexamethasone could be substituted for another steroid as follows: Dexamethasone 0.75 mg = Methyl-prednisolone 4 mg= Prednisone/prednisolone 5 mg= Hydrocortisone 20 mg= Cortisone 25 mg	From Eisenberger et al. (2004) [36]: I(1)+I(2): 47% (P<0.0001) Duration (median months): I(1): 7.7 (95% CI:7.1-8.6) I(2): 8.2 (95% CI:6.3-11.5) C: 7.8 (95% CI:5.4-10.5) **Outcome 5: Adverse events** (%) (measured using the Common Toxicity Criteria of the National Cancer Institute, version 2) (N=997) |	I(1) (n=332)	I(2) (n=330)	C (n=335)
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Grade 3-4Anaemia	5	5	2
Grade 3-4 Thrombocytopenia	1	0	1
Grade 3-4 Neutropenia	32*	2†	22
Febrile neutropenia	3	0	2
Impaired LVEF	10†	8†	22
Major decrease in LVEF	1†	2*	7
Fatigue	53†	49†	35
Grade 3-4 Fatigue	5	5	5
Alopecia	65†	50†	13
Nausea/ vomiting	42	41	38
Diarrhoea	32†	34†	10
Nail changes	30†	37†	7
Sensory neuropathy	30†	24†	7
Anorexia	17	21*	14
Change in taste	18†	24†	7
Stomatitis	20†	17†	8
Myalgia	14	14	13
Dyspnea	15*	14*	9
Tearing	10†	21†	1
Peripheral oedema	19†	12†	1
Epistaxis	6	17†	2
≥1 serious adverse event	26	29	20
Treatment related death	0.3	0.3	1 | *P≤0.05 in comparison with C †P≤0.0015 in comparison with C	

	limit of normal range, serum alanine aminotransferase, aspartate aminotransferase and creatine levels ≤1.5 times upper limit of the normal range. Patients were required to have stable levels of pain for at least 7 days before randomisation (defined by daily variation of no more than 1 in PPI score or 25% in analgesic score).	**Protocol deviations:** Crossovers: 27% randomised to I(1) received C. 24% randomised to I(2) received C. 20% randomised to C received docetaxel.	From Eisenberger et al. (2004) [36]: I(1) / I(2) / C Overall grade 3/4: 45.8 / 43 / 34.6 Bone pain grade 3/4: 7.8 / 7.3 / 9.9 Infection grade 3/4: 5.7 / 5..5 / 4.2 Diarrhoea grade 3/4: 2.1 / 4.8 / 1.2 Further adverse events reported in Dagher et al. (2004)[34]: I(1) / C Infection: 32 / 20 Grade 3-4 Infection: 6 / 4 Allergic reactions: 8 / 1 Grade 3-4 Allergic reactions: 1 / 0 Fluid retention: 24 / 5 Grade 3-4 Fluid retention: 1 / 0 Weight gain: 8 / 3 Grade 3-4 Weight gain: 0 / 0 Motor neuropathy: 7 / 3 Grade 3-4 Motor neuropathy: 2 / 1 Rash/desquamation: 6 / 3 Grade 3-4 Rash/desquamation: 0 / 1 Cough: 12 / 8 Grade 3-4 Cough: 0 / 0 Arthralgia: 8 / 5 Grade 3-4 Arthragia: 1 / 1 Anaemia: 67 / 58 Neutropenia: 41 / 48 From Centre for Drug Evaluation and Research (2004)[37]: The following adverse events occurred at a rate of 10% or higher in patients over 65 compared to younger patients: Anaemia (70.7% vs 59.3%) Infection (37& vs 24.2%) Nail changes (33.7% vs 22.6%) Anorexia (20.7% vs 9.7%) Weight loss(15.4% vs 4.8%)	

			Outcome 6: Pain Pain relief: A two-point reduction in the PPI score from baseline, without an increase in the analgesic score, or vice versa, maintained for at least 3 weeks. Number evaluated: (N=464) I(1): 153; I(2): 154; C:157 Response rate: I(1): 35% (95% CI:27-43, P=0.01) I(2): 31% (95% CI:24-39, P=0.08) C: 22% (95% CI:16-29) Duration (median months): I(1): 3.5 (95% CI:2.4-8.1) I(2): 5.6 (95% CI:2.8-6.8) C: 4.8 (95% CI:4.4-indeterminate) **Outcome 7: Health related QoL** 16-point improvement from baseline in the FACT-P score on two measurements obtained at least 3 weeks apart. Number evaluated: (N=815) I(1): 278; I(2): 270; C: 267 Response rate: I(1):22% (95% CI:17-27, P=0.009) I(2): 23% (95% CI:18-28, P=0.005) C: 13% (95% CI:9-18) **Withdrawals:** I(1): 3 patients did not receive chemotherapy. I(2): 4 patients did not receive chemotherapy. C: 2 patients did not receive chemotherapy. **Discontinuations:** I(1): 38% patients stopped treatment due to progression of disease, 11% due to adverse events. I(2): 35% patients stopped treatment due to progression of disease, 16% due to adverse events. C: 56% patients stopped treatment due to progression of disease, 10% due to adverse events.	

			From Industry Submission: **Number of cycles:** Median (range) I(1): 9.5 (1-11) I(2): 4 (1-6) C: 5 (1-11) Dose reductions (%) I(1): 12; I(2): 9; C: 8	

Study Details and Design	Participant Details	Intervention Details	Results	Conclusion and Comments
Author: Oudard et al. (2005)[28] **Country:** France (24 centres). **Primary source:** Handsearch (reference list of industry submission) **Aim:** To evaluate PSA response and safety of two Docetaxel-Estramustine-Prednisone schedules and one Mitoxantrone-Prednisone schedule. **Trial ID:** **Phase:** II **Length of follow-up:** Not stated **Number and times of follow-up measurements:** Patients were evaluated radiographically every 2 cycles and/or by radionuclide bone cycle every 3 cycles and then every 3 months whilst in the study. Weekly complete blood count (CBC) and 3-weekly PSA levels were measured during treatments. Pain control and analgesic consumption were self-reported using pain diaries and medication records were checked.	**Number randomised:** 130, 127 included in the analysis. **Disease characteristics: (N=127)** ECOG performance status: 0: I(1) 17 (40%); I(2) 25 (59%); C 20 (48%) 1: I(1) 19 (44%); I(2) 13 (31%); C 11 (26%) 2: I(1) 7 (16%); I(2) 4 (10%); C 11 (26%) Gleason Score: 2-4: I(1) 2 (5%); I(2) 0; C 1 (2%) 5-6: I(1) 10 (23%); I(2) 5 (12%); C 10 (24%) 7-10: I(1) 30 (70%); I(2) 37 (88%); C 28 (67%) Unknown: I(1) 1 (2%); I(2) 0; C 3 (7%) Tumour related symptoms: No bone pain: I(1) 12 (28); I(2) 12 (29); C 11 (26) Bone Pain: I(1) 28 (65); I(2) 24 (57); C 30 (72) Unknown: I(1) 3 (7); I(2) 6 (14); C 1 (2)	**Intervention 1:** Docetaxel, estramustine + prednisone. **No. randomised:** 44, 43 assessed. **Route of administration:** Docetaxel: 1-hour i.v. infusion; Estramustine: p.o. 2 hours after meals; prednisone: not stated. **Dose:** docetaxel: 70 mg/m^2 on day 2 every 21 days; estramustine: 840 mg in 3 divided doses on days 1 to 5 and days 8 to 12; prednisone: 10 mg daily. **No. of cycles:** Not stated. **Length per cycle:** 3 weeks. **Intervention 2:** Docetaxel, estramustine + prednisone. **No. randomised:** 44, 42 assessed. **Route of administration:** Docetaxel: 30-minute i.v. infusion; Estramustine: p.o. 2 hours after meals; prednisone: not stated. **Dose:** docetaxel: 35 mg/m^2 on days 2 and 9 every 21 days; estramustine: 840 mg in 3 divided doses on days 1 to 5 and days 8 to 12; prednisone: 10 mg daily. **No. of cycles:** Not stated. **Length per cycle:** 3 weeks. **Control:** Mitoxantrone + prednisone	**Outcome 1: Overall survival** (n=127) Defined as the time from study entry to death or date of last follow-up: I(1): 18.6 months (95% CI: 14.9-22.3) I(2): 18.4 months (95% CI: 14.1-22.8) C: 13.4 months (95% CI: 9.4-17.5) Survival analysis was performed at 12 months median follow-up (95% CI: 10.1, 13.8) when 99 deaths (78%) had occurred. 3-year survival was 22% for entire cohort. Relative event rates: I(1) vs C: 1.08 (95% CI: 0.66-1.76) I(2) vs C: 0.75 (95% CI: 0.46-1.21) I(1) vs I(2): 1.43 (95% CI: 0.89-2.31) P=0.13 Association of median overall survival with baseline characteristics (multiivariate): Baseline ECOG performance status: P=0.0001 Baseline haemoglobin level: P=0.006 Relative risk of death reduction (Hazard Ratios): I(1) and C: 6% (95% CI: -2%-71%) I(2) and C: 14% (95% CI: -8%-32%). **Outcome 2: Progression-free survival** Median time to progression (defined as the date of the first computed tomography scan demonstrating a new lesion(s) or a ≥25% increase in the bi-dimensional measurements of previously measurable disease. For those with bone disease, new lesion(s) on radionuclide bone scan counted as disease progression. Median time for those with measurable disease: 11.5 months (95% CI: 6.9-16.9) Median time for those with bone disease only: 18.2 months (95% CI: 16.5-21.8)	**Authors' conclusions:** The results show significantly higher PSA decline (≤50%) and longer times to progression in patients with hormone-refractory prostate cancer receiving docetaxel-estramustine-prednisone based chemotherapy than mitoxantrone-prednisone based chemotherapy, and that docetaxel-estramustine-prednisone based chemotherapy could be proposed in this setting. **Comments:** Two authors (including lead author) have disclosed potential conflicts of interest with Aventis. One of the additional abstracts identified (Oudard et al. (2003)[40]) had conflicting results to the main trial report, therefore was not used for data extraction.

Method of randomisation:
-Assignment: Centralised at the Georges Pompidou Oncology Data Center. Patients were stratified according to baseline PSA level (≤150 vs ≥150 ng/mL) and ECOG performance status (0 vs 1-2).
-Allocation:

ITT analysis performed: Modified ITT-patients who received at least 1 treatment cycle were assessable for response and toxicity (n=127).

Per protocol analysis performed: Not stated.

Comments:
A Simon design was used to calculate that a sample size of 130 was required to distinguish a 60% PSA response from a 30% response with 80% power and a type 1 error of 0.05.

Baseline comparability: Yes, non-significant trend for I(2) to have better ECOG performance status (P=0.18).

Eligibility criteria specified: Yes.

Co-interventions: Pre-medication with oral prednisolone, 300 mg total dose and oral warfarin 2 mg/d administered

Analgesic use at entry:

	I(1) n(%)	I(2) n(%)	C n(%)
Treatment	24 (56)	21 (50)	25 (60)
No treatment	16 (37)	14 (33)	16 (38)
unknown	3 (7)	7 (17)	1 (2)

Serum PSA (ng/mL), median (IQ range):
I(1): 71 (1.9-2818)
I(2): 69.5 (0.01-2416)
C: 77.7 (0.41-1840)

Sites of metastases:

	I(1) n(%)	I(2) n(%)	C n(%)
Bone	38 (88)	39 (93)	41 (98)
Lymph Nodes	16 (37)	11 (26)	13 (31)
Other	5 (12)	8 (19)	3 (7)

Previous treatments:
Number of previous hormonal regimens:

	I(1) n(%)	I(2) n(%)	C n(%)
One	30 (70)	26 (62)	32 (76)
Two	11 (25)	12 (29)	10 (24)
three	2 (5)	4 (9)	0

Other previous anticancer therapy:

	I(1) n(%)	I(2) n(%)	C n(%)
Surgery	6 (14)	10 (24)	8 (19)
Radio-therapy	10 (23)	9 (21)	7 (17)

No. randomised: 42, 42 assessed.
Route of administration: Mitoxantrone: 30-minute i.v. infusion; prednisone: not stated.
Dose: Mitoxantrone: 12 mg/m^2 on day 1 every 21 days; prednisone: 10 mg daily.
No. of cycles: Not stated.
Length per cycle: 3 weeks.

Comments about intervention/control: The planned dose-intensity for docetaxel in both I(1) and I(2) was 23.3 mg/m^2/week. Dose reductions of docetaxel to 60 mg/m^2 in I(1) and to 30 mg/m^2 in I(2) were made if significant toxicity occurred.

Crossovers from I(1) or I(2) to C and from C to I(1) or I(2) were allowed in patients failing to respond to primary treatment.

Protocol deviations: 3 patients never started treatment (1 stroke and 2 withdrawals of consent).

Outcome 3: Response rate N=127
Measurable disease response was defined in accordance with WHO guidelines.

I(1):9 responses (7 partial responses (PRs), 2 complete responses (CRs))
I(2): 3 responses (2 PRs, 1CR)
C: 1 response (1 CR)
P=0.01
(Bonferroni, P=0.016 between I(1) and C)

Outcome 4: PSA Decline (n=123, 1 patient in I(2), 3 in C not evaluated due to baseline PSA<4ng/mL)
(Primary outcome of trial).

PSA decrease (≥50%) was documented in accordance with the guidelines of the PSA Working Group:

	I(1)	I(2)	C
≥ 50%*	29 (67%)	26 (63%)	7 (18%)
≥ 75%*	22 (51%)	16 (39%)	3 (8%)
Normalisation^ (<4ng/mL)	10 (23%)	7 (17%)	1 (2%)

*P<0.0001, between all groups (bonferroni P<0.002 between I(1) and C; I(2) and C).
^P=0.02 between all groups (bonferroni P=0.01 between I(1) and C).

Median time to PSA progression (from date of randomisation to the date of progression; defined by a ≥25% increase in PSA level from baseline or ≥50% increase in PSA level from the lowest value achieved, provided that the increase was at least 5 ng/mL, confirmed by 3 successive measurements at 3-weekly intervals):

I(1): 8.8 months (95% CI: 6.9-10.8)
I(2): 9.3 months (95% CI: 7.5-11.1)
C: 1.7 months (95% CI: 0.7-2.7)
P=0.000001

Relative event rates:
I(1) vs C: 0.44 (95% CI: 0.25-0.76)
I(2) vs C: 0.35 (95% CI: 0.20-0.60)
I(1) vs I(2): 1.26 (95% CI: 0.85-1.89)
P=0.00001

continuously in I(1) and I(2).

From Oudard et al. (2002)[38] Oudard et al.[39]: Coumadin (2 mg p.o.) given continuously to all patients.

Blinding:
- **Outcome assessor:** Not stated.
- **Carer:** No.
- **Patient:** No.
- **Success assessed:** N/A.

80% Follow-up: Yes.

Median age of participants:
I(1):68; I(2): 68; C: 70

Age IQ range of participants:
I(1): 52-91; I(2): 51-79; C: 52-85

Other participant characteristics:
Time from diagnosis to random assignment (median months, IQ range):
I(1): 33, 3-219
I(2):33, 5-151
C: 47, 6-150

Time from start of hormonal treatment to random assignment (median months, IQ range):
I(1): 16, 2-116
I(2): 27, 2-89
C: 25, 1-118

Comments about participants:

Inclusion/exclusion criteria:
Histologically proven metastatic adenocarcinoma of the prostate with progressive disease, despite androgen deprivation. Antiandrogen withdrawal and documented disease progression were required before study entry. Disease progression was defined as appearance of new lesion (s), and/or an increase of ≥25% of measurable metastases, and/or the appearance of new foci on a radionuclide bone scan, and/or 3 consecutive increases in PSA at least 1 week apart in the presence of testosterone castrate level of metastatic patients. Patients were ineligible if they had received prior chemotherapy (including Estramustine), and at least 4 weeks had to have elapsed since completion of radiation, or last dose of a therapeutic radionuclide, and prior flutamide or nilutamide. Six weeks had to have elapsed since prior bicalutamide.

Median duration of PSA response, in months (defined as the time interval between the first 50% decline in PSA levels until PSA increased to 50% above the nadir):

I(1): 8; I(2): 8.3 ; C: 6.4

Outcome 5: Adverse events (n=127)
Scored according to the revised National Cancer Institute Common Toxicity Criteria, version 1.

Severe adverse events (grade 3 or 4):

	I(1): n(%)	I(2): n(%)	C: n(%)
Granulocytopenia	16 (37)	0	20 (48)
Granulocytopenic fever	0	0	3 (7)
Anaemia	1 (2)	0	3 (7)
Thrombocytopenia	0	1 (2)	1 (2)
Nausea	1 (2)	0	0
Vomiting	1 (2)	0	0
Diarrhoea	3 (7)	0	0
Thrombosis (caused by estramustine)	3 (7)	3 (7)	0

I(1):1 corticosteroid premedication-related death reported.

Other adverse events:
Asthenia:

I(1): 47%; I(2): 41%; C: 26%
P=0.30
Nail and skin toxicities:
I(1)+I(2): 14%.
Decrease in LVEF (grade 1 or 2):
C: 4 (10%).

Outcome 6: Pain (n=127)
'Clinical benefit' was measured using the pain control and analgesic consumption indices of the McGill pain questionnaire and ECOG performance status. Pain control was scored from 0 (no pain) to 4 (uncontrollable pain) and the analgesic consumption was scored from 0 (no requirement) to 4 (regular, narcotic analgesic use). Clinical benefit was defined as reduction by at least 1 in the pain index and/or performance status improvement by at least 1.

	Patients were also required to have life expectancy at least 3 months, ECOG performance score of 0 to 2, and no uncontrolled diabetes or other comorbidities that may limit survival. Patients were also required to have a castrated level of testosterone (<50 ng/mL) achieved by bilateral orchidectomy or LHRH. Laboratory criteria were: granulocyte count ≥ 1.5 x 10^9/L, platelet count ≥100 x10^9/L, haemoglobin ≥10 g/dL, total serum bilirubin of ≤1.5 x institutional upper limit of normal, transaminases ≤1.5 x upper limit of normal, alkaline phosphatase < 2 x upper limit of normal, creatinine ≤ 1.5 x upper limit of normal.			

	I(1) n(%)	I(2) n(%)	C n(%)
Pain control	10 (23)	9 (21)	7 (17)
Analgesic consumption	15 (35)	10 (24)	6 (14)
Improved pain index 1+2	17 (40)	12 (29)	7 (17)
Improved ECOG	26 (60)	20 (48)	12 (28)*
Improved clinical benefit 3+4	14 (33)	10 (24)	9 (21)

*P=0.01

Outcome 7: Health related QoL
Not reported.

Withdrawals:
3 patients randomised were never treated, 1 had a stroke before first cycle of treatment and 2 withdrew their consent.

Discontinuations:
4 patients were taken off therapy due to severe adverse side effects.

Median relative dose-intensities:
I(1), docetaxel: 1.0 (range: 0.58-1.07)
I(2),docetaxel: 0.98 (range: 0.50-1.11)
C, mitoxantrone: 0.97 (range:0.33-1.17)

Median cumulative dose:
I(1): 414 mg/m^2 (range: 69-429)
I(2): 403 mg/m^2 (range: 66-423)
C: 66 mg/m^2 (range: 10-76)

The Estramustine cumulative doses were similar in the docetaxel arms.

Dose reductions required in 2.4% of patients (2 in I(1), 1 in C).

Level of crossover:
I(1): 16%; I(2): 10%; C: 48%
P=0.00001, between groups.

Median time on primary treatment:
I(1): 20.4 months (95% CI: 17.5-23.3)
I(2): 19.2 months (95% CI: 15.7-22.8)

			C: 11.6 months (95% CI: 7.1-16.2) P=0.003 **Relative event rates for time on primary treatment:** I(1) vs C: 0.49 (95% CI: 0.25-0.97) I(2) vs C: 0.39 (95% CI: 0.20-0.76) I(1) vs I(2): 1.26 (95% CI: 0.78-2.04) P=0.0005. *Exploratory analysis:* Survival of patients in C receiving salvage therapy of docetaxel: 31.7 months (95% CI: 26.4-36.9 months) Survival of patients in C receiving no further therapy or non-docetaxel chemotherapy: 7.5 months (95% CI: 4.9-10.1 months)	

Study Details and Design	Participant Details	Intervention Details	Results	Conclusion and Comments
Author: Petrylak 2004[29] **Country:** USA **Primary source:** Hand searching **Aim:** To determine whether docetaxel plus estramustine improves survival over that afforded by mitoxantrone plus prednisone in men with androgen-independent prostate cancer. **Trial ID:** SWOG 9916 **Phase:** Phase III **Length of follow-up:** Median: 32 months. **Number and times of follow-up measurements:** Every 6 months for 2 years then annually for 1 year. **Method of randomisation:** **-Assignment:** Not stated **-Allocation:** Not stated Patients were stratified by type of progression (measurable vs PSA alone), grade of bone pain (mild, moderate, severe, disabling), and SWOG performance-status (0-1 vs 2-3). **ITT analysis performed:** Yes.	**Number randomised:** 770 men, 674 eligible. **Sites of disease:** Bone: I=84%; C=88% Lymph node: I=24%; C=26% Liver: I=8%; C=9% Lung: I=10%; C=10% **Disease characteristics:** SWOG performance status: I: 0-1=90%; 2-3=10%. C: 0-1=88%; 2-3=12%. PSA (ng/ml), Median (range): I: 84 (0.1-10,820) C: 90 (0.1-8,378) Bone pain, Grade <2: I: 64%; C: 64% Type of progression: Measurable: I: 81%; C: 82%. Increased PSA only: I: 19%; C: 18%. **Previous treatments:** Prior radiotherapy (to <30% of the bone marrow only) or one prior systemic therapy (except with estramustine, taxanes, anthracyclines, or mitoxantrone) was permitted if at least four weeks had elapsed since the completion of that therapy. Antiandrogen therapy and bisphosphonates were discontinued at least 4 weeks before registration. **Median age of participants:** 70 years **Age range of participants:**	**Intervention:** 280 mg estramustine 3xdaily on days 1-5, + 60 mg docetaxel per m^2 body-surface area i.v. on day 2, preceded by 60 mg dexamethasone orally in 3 doses. Given in 21-day cycles. Dose of docetaxel increased to 70 mg/m^2 if no grade 3-4 adverse events during first cycle. Protocol change: Adding 2 mg warfarin + 325 mg aspirin/day. Treatment continued until disease progression or unacceptable adverse events, or until max. 12 cycles of docetaxel+estramustine administered. **No. randomised:** 386 (338 eligible) **Route of administration:** estramustine not reported; docetaxel: i.v. **Dose:** 280 mg estramustine; 60-70 mg/m^2 docetaxel. **No. of cycles:** 12 **Length per cycle:** 21 days **Control:** 12 mg mitoxantrone per m^2 body-surface area i.v. on day 1, + 5 mg prednisone 2xdaily. Given in 21-day cycles. Dose of mitoxantrone increased to 14 mg/m^2 if no grade 3-4 adverse events	**Outcome 1: Overall survival** Time from the date of randomisation to the date of death from any cause or censored at the date of last contact. Median survival: (N=674) I: 17.5 months (P=0.02) C: 15.6 months HR for death: 0.80 (95% CI: 0.67-0.97) After median follow-up of 32 months: I: 217/338 (64%) died C: 235/336 (70%) died **Outcome 2: Progression-free survival** Time from randomisation to the first occurrence of objective or PSA progression or death from any cause. Progression was defined by one of the following: 50% increase or 10 cm, whichever was smaller, in the sum of measurements of metastatic lesions over the sum at baseline; a clear worsening of non-measurable disease; reappearance of any lesion that had disappeared; appearance of a new lesion; or death. Median time to progression: (N=674) I: 6.3 months (P=<0.001) C: 3.2 months **Outcome 3: Response rate** Objective responses were defined on the basis of the sum of bi-dimensional measurements of metastatic lesions. Confirmed objective response required a follow-up scan (min of 4 weeks later) that demonstrated a continued response. Partial response: (N=196) I: 17% (17/103, 4 unconfirmed) C: 11% (10/93, 4 unconfirmed) Not significant (P=0.30) RR=0.65 (95% CI: 0.314-1.346)	**Authors' conclusions:** The improvement in median survival of nearly two months with docetaxel and estramustine, as compared to mitoxantrone plus prednisone, provides support for this approach in men with metastatic androgen-independent prostate cancer. **Comments:** The SWOG Statistical Centre received funding from Aventis Pharmaceuticals for the additional cost of collecting data on the quality of life. Aventis was allowed to review the protocol and make comments before enrolment began. Aventis had no access to the data but received a semi-annual summary of enrolment and adverse events.

Per protocol analysis performed: Not stated.

Comments:

Baseline comparability: Adequate

Eligibility criteria specified: Yes

Co-interventions: Pre-medication with dexamethasone was given in the intervention group. The intervention group was also given warfarin and aspirin after a protocol change on 15/1/01. To ensure continued androgen ablation, patients continued taking luteinizing-hormone releasing hormone agonists throughout study treatment.

Blinding:
- **Outcome assessor:** Not stated
- **Carer:** Not stated
- **Patient:** Not stated
- **Success assessed:** No

80% Follow-up: Yes

I: 47-88 years; C: 43-87 years.

Other participant characteristics:
Race:
White: I=86%; C=82%
Black: I=12%; C=15%
Hispanic: I=7%; C=6%
Asian: I=1%; C=1%
Unknown: I=1%; C=1%

Comments about participants:

Inclusion/exclusion criteria:
Pathologically confirmed adeno-carcinoma of the prostate and progressive metastatic disease (stage D1 or D2) despite androgen-ablative therapy and cessation of anti-androgen treatment.

Criteria for progressive disease were progression of a bi-dimensionally measurable lesion, as assessed within 28 days before study registration; progression of disease that could be evaluated but not measured (eg by bone scanning), as assessed within 42 days before registration; or an increase in serum PSA level over the baseline level in at least two consecutive samples obtained at least 7 days apart.

Adequate renal, hepatic, and cardiac function and a SWOG performance-status score of 0 to 2 (3 was allowed if due to bone pain) were also required.

Patients were ineligible if they had received prior radioisotope or anticoagulant therapy (excluding aspirin), had active thrombophlebitis or hyper-coagulability, had a history of pulmonary embolus, or pleural effusions or ascites.

during first cycle.
Treatment continued until disease progression or unacceptable adverse events, or until 144 mg/m^2 mitoxantrone administered.

No. randomised: 384 (336 eligible)
Route of administration: mitoxantrone: i.v.; prednisone not reported.
Dose: 12-14 mg/m^2 mitoxantrone
No. of cycles: 12
Length per cycle: 21 days

Comments about intervention/control:

Protocol deviations:
Warfarin and aspirin were added to the intervention group due to a report that prophylactic anticoagulation decreased estramustine-associated vascular effects (15 Jan 2001). Numbers of patients enrolled before/after this date not reported. Enrolment from Oct 1999 to Jan 2003.

There were 11 major protocol deviations. Six in I and 4 in C did not receive the assigned treatment and were not included in the evaluation of adverse events. One man received intermittent radiotherapy while on C, he was included in the evaluation of adverse events.

Outcome 4: PSA decline
PSA decline of ≥50%: (N=612)
I: 155/309 (50%)
C: 82/303 (27%)
(P<0.001)

Outcome 5: Adverse events
Adverse events (measured using the Common Toxicity Criteria of the National Cancer Institute, version 2; grade 3 (severe)/4 (life-threatening)/5 (fatal): (N=658)

	I (n=330)	C (n=328)
Drug reaction	0/0/3	0/0/3
Cardiovascular*	37/10/1	16/6/0
Clotting	2/0/0	0/0/0
Dermatologic	1/0/0	1/0/0
Endocrine	0/0/0	1/0/0
Influenza-like	29/3/0	20/2/0
Nausea/vomiting*	61/5/0	16/1/0
Hematologic	17/47/1	18/33/0
Hemorrhage	11/2/1	6/0/0
Immounologic	3/0/0	0/0/0
Infection*	36/7/2	20/2/0
Liver	9/1/1	11/1/0
Lung	12/2/1	8/1/1
Metabolic*	14/6/0	2/0/0
Musculoskeletal	8/0/0	1/2/0
Neurologic*	21/2/0	5/0/0
Pain	34/1/0	18/5/0
Renal/bladder	8/0/1	3/0/0
Max. grade of any*	114/62/8	63/46/4

*= p<0.005

The rate of grade 3, 4 or 5 neutropenia in the docetaxel group did not differ significantly from that in the mitoxantrone group (16.1% versus 12.5%; P=0.22). However, the docetaxel group had significantly higher rates of grade 3 or 4 neutropenic fevers (5% versus 2%; P=0.01).

There were eight treatment related deaths in the docetaxel group and 4 in the mitoxantrone group.

			Outcome 6: Pain No significant difference (data not shown). (N=Not stated) **Outcome 7: Health related QoL** Not reported. **Withdrawals:** I: 48 (not eligible) 54/338 (16%) due to adverse events. C: 48 (not eligible). 32/336 (10%) due to adverse events. **Discontinuations:** Six patients who discontinued treatment within one week after starting I (2) or C (4) were not included in the evaluation of adverse events.	

<table>
<tr><th>Study Details and Design</th><th>Participant Details</th><th>Intervention Details</th><th>Results</th><th>Conclusion and Comments</th></tr>
<tr>
<td>Author: Berry et al. (2002)[30]

Country: USA

Primary source: MEDLINE

Aim: To compare median time to treatment failure of men with asymptomatic hormone-refractory progressive prostate cancer treated with mitoxantrone plus prednisone versus prednisone alone.

Trial ID:
Phase: III

Length of follow-up:
Median: 21.8 months (range: 2.4-50)

maximum planned: 4 years

Number and times of follow-up measurements:.Blood count/platelet & liver function every wk for 1st cycle and before each subsequent cycle. PSA every other cycle through cycle 6, every 3 months after cycle 6 and at study termination. Physical examination, tumour assessment & ECOG at end of every cycle. Radiologic assessments at the end of cycle 6, every 3 months if PSA > 50% over baseline and at study termination.</td>
<td>Number randomised: 120, 119 included in analysis

Disease characteristics:
Diagnosis stage
<table>
<tr><th></th><th>I: n (%)</th><th>C: n (%)</th></tr>
<tr><td>A</td><td>2 (4)</td><td>5 (8)</td></tr>
<tr><td>B1</td><td>4 (7)</td><td>2 (3)</td></tr>
<tr><td>B2</td><td>10 (18)</td><td>9 (14)</td></tr>
<tr><td>C1</td><td>3 (5)</td><td>9 (14)</td></tr>
<tr><td>C2</td><td>5 (9)</td><td>2 (3)</td></tr>
<tr><td>D1</td><td>9 (16)</td><td>13 (21)</td></tr>
<tr><td>D2</td><td>19 (33)</td><td>21 (34)</td></tr>
<tr><td>D3</td><td>1 (2)</td><td>0</td></tr>
<tr><td>unknown</td><td>3 (5)</td><td>2 (3)</td></tr>
</table>
Pretreatment tumour characteristics
<table>
<tr><th>Tumour</th><th>I: n (%)</th><th>C: n (%)</th></tr>
<tr><td>Measurable</td><td>8 (14)</td><td>9 (14)</td></tr>
<tr><td>PSA only</td><td>2 (4)</td><td>5 (8)</td></tr>
<tr><td>Non-measurable and increased PSA</td><td>46 (82)</td><td>49 (78)</td></tr>
</table>
<table>
<tr><th>Metastases</th><th>I: n (%)</th><th>C: n (%)</th></tr>
<tr><td>Bone</td><td>48 (86)</td><td>50 (79)</td></tr>
<tr><td>Lymph</td><td>10 (18)</td><td>11 (18)</td></tr>
<tr><td>Lung</td><td>1 (2)</td><td>4 (6)</td></tr>
<tr><td>Liver</td><td>2 (4)</td><td>0</td></tr>
</table>
PSA at study entry:
I: median: 56.7 (range: 3.7 – 2,375 ng/ml)
C: median: 71.0 (range: 1.1 – 1,233 ng/ml)

Previous treatments:</td>
<td>Intervention: Mitoxantrone + prednisone

No. randomised: 56
Route of administration: mitoxantrone: i.v.; prednisone: p.o.
Dose: mitoxantrone: 12 mg/m2 every 3 weeks; prednisone 5 mg b.i.d.
No. of cycles: 6
Length per cycle: 3 weeks

Control: Prednisone

No. randomised: 63
Route of administration: p.o.
Dose: 5 mg b.i.d.
No. of cycles: Not stated
Length per cycle: Not stated

Comments about intervention/control:
Prednisone continued even after mitoxantrone therapy was stopped. Maximum of 2, 25% dose reductions of mitoxantrone allowed.

Supportive care was administered at the discretion of the investigator. Hematopoietic growth factors were administered according to ASCO guidelines as needed.

Protocol deviations:</td>
<td>Outcome 1: Overall survival (N=119)
I: median = 23 months (range:3-49)
C: median = 19 months (range: 2-50)
No significant difference

Median survival for subgroup - PSA responders (response = ≥50% reduction in PSA levels for ≥ 2 months with stabilisation or improvement of performance status for ≥ 2 weeks.)
<table>
<tr><th></th><th>I: months</th><th>C: months</th></tr>
<tr><td>Responders</td><td>31.8</td><td>32.9</td></tr>
<tr><td>Non-responders</td><td>18.3</td><td>18.3</td></tr>
</table>
Died within 4 years of study beginning
I: 43 (77%); C: 48 (76%)

Survival at 12 months
I: 82%; C:76%

Survival at 24 months
I: 45%; C: 44%

Outcome 2: Progression-free survival (N=119)
(after 12 months)
I: 36%; C: 15%

(after 24 months)
I: 13%; C: 10%

Time to treatment failure; primary outcome of trial (aggregate end-point of time to disease progression, removal from study or time to initiation of alternative therapy from start of treatment. Time to progression = time to treatment failure):

I: median: 8.1 months (range: 1-50)
C: median: 4.1 months (range: 1-37)
(P=0.018)

From Gregurich et al.[44]:
Median time to progression:
I: 10.5 months; C: 3.8 months (P<0.001)</td>
<td>Authors' conclusions: Patients with asymptomatic progressive disease had a significantly higher response rate when treated with mitoxantrone plus prednisone, than when treated with prednisone alone, measured by a ≥ 50% decrease in PSA. Time to treatment failure in the I group was also significantly longer but survival rates were not affected.

Comments: Supported by Immunex corporation. Lead author has financial links to Bristol Myers Squibb, Immunex & Aventis.</td>
</tr>
</table>

Patients completing treatment followed every 3 months for progression & survival. Patients with disease progression or who withdrew from study followed only for survival.

Method of randomisation:
-Assignment: Not reported
-Allocation: Not reported

ITT analysis performed: No data available for 1 patient, 119 analysed

Per protocol analysis performed:
Not stated.

Comments: All patients given at least 1 dose included in analysis of safety. Study did not allow for crossovers.

Baseline comparability: Yes

Eligibility criteria specified: Yes

Co-interventions: Anti-androgens where previously given. All other forms of hormone therapy were disallowed.

Blinding:
- **Outcome assessor:** No
- **Carer:** No
- **Patient:** No
- **Success assessed:** N/A

Radical prostatectomy
I: 27 (48%)
C: 38 (60%)

Definitive local radiotherapy
I: 36 (64%)
C: 35 (56%)

Median age of participants:
I(1): 70; C: 74.
Age range of participants:
I(1): 49-87; C: 51-90

Other participant characteristics:
ECOG Performance status:
I: 0: 42 (75%); 1: 13 (23%); 2: 1 (2%)
C: 0: 47 (75%); 1: 16 (25%); 2: 0

Comments about participants:

Inclusion/exclusion criteria:
Asymptomatic hormone-refractory adenocarcinoma that had progressed on at least 1 hormonal regimen (orchiectomy, LHRH analogue or diethylstilbestrol). Disease progression defined as 2-fold or greater increase in PSA over 2 determinations; 25% increase in no. of bone scan lesions or 25% increase in size of soft tissue lesions.

At least 4 weeks had to have elapsed since antiandrogen treatment, systemic corticosteroid therapy or radiotherapy or at least 3 weeks since major surgery. Absolute neutrophils count ≥ 1,500/µl; platelet count ≥ 150,000/µl; haemoglobin ≥ 9gm/dl.

Patients were also required to have adequate pre-treatment liver and cardiac function and ECOG performance status of 0 – 2. No other malignancy in last 5 years, parenchymal brain metastases,

Subgroup- PSA responders (response = ≥50% reduction in PSA levels for ≥ 2 months with stabilisation or improvement of performance status for ≥ 2 weeks.)

	I: months (range)	C: months (range)
Responders	13.5 (3.5-46.5)	11.7 (6.5-46)
Non-responders*	6.9 (1.1-35)	3.2 (0.9-34.5)

*P=0.007

Outcome 3: Response Rate
Used PSA decline as a marker for disease response (see below). "Objective responses" for those with measurable tumours (N=17, I: 8; C:9):
No complete responses.
Partial responses:
I: 2 (25%); C: 2 (22%)

Outcome 4: PSA decline (N=119)
≥50% reduction in PSA levels for ≥ 2 months with stabilisation or improvement of performance status for ≥ 2 weeks.
I: 27 (48%); C: 15 (24%)
P = 0.007

Median time to ≥50% response:
I: 2.2 months (range: 0.6 -4.6)
C: 2.2 months (range: 0.2 – 7.1)

Outcome 5: **Adverse events**
Drug-related toxicities at > grade 3

	I: n (%)	C: n (%)
Neutropenia	27 (48)	6 (10)
Leukopenia	11 (20)	5 (8)
Pulmonary	4 (7)	4 (6)
Asthenia	3 (5)	3 (5)
Renal	1 (2)	3 (5)
GI	3 (5)	1 (2)
Sepsis	2 (4)	0
Melanoma	1 (2)	0

Some patients had > 1 toxic reaction.

Outcome 6: Pain
Not reported

80% Follow-up: Yes	prior immunotherapy, prior chemotherapy or concurrent use of exogenous corticosteroids.		**Outcome 7: Health-related QoL** Not reported **Discontinuations:** Not stated.	

<table>
<tr><th>Study Details and Design</th><th>Participant Details</th><th>Intervention Details</th><th>Results</th><th>Conclusion and Comments</th></tr>
<tr>
<td>Author: Tannock et al. (1996)[31]

Country: Canada

Primary source: Medline
Aim: To investigate the benefit of chemotherapy in patients with symptomatic hormone-resistant prostate cancer using relevant end-points of palliation.

Trial ID: CCI-NOV22
Phase: III

Length of follow-up: Not Stated

Median: Not Stated

Number and times of follow-up measurements:
Blood tests and QoL and pain questionnaires every 3 weeks, including the prostate-cancer specific quality of life instrument (PROSQOLI), the European organisation for Research and Treatment of Cancer (EORTC) and the Present Pain Intensity scale (PPI). Bone scans and radiographs every 3 months. Blood cell counts repeated on days 10&14 of 1st cycle, and once between days 10 and 14 in cycles thereafter. A daily analgesia diary was also kept by patients.</td>
<td>Number randomised: 161
Disease characteristics:
Sites of metastasis
<table><tr><td>Site</td><td>I: n (%)</td><td>C: n (%)</td></tr><tr><td>Bone</td><td>78 (98)</td><td>77 (95)</td></tr><tr><td>Lymph</td><td>18 (22)</td><td>15 (19)</td></tr><tr><td>Visceral</td><td>3 (4)</td><td>3 (4)</td></tr><tr><td>Other</td><td>7 (9)</td><td>8 (10)</td></tr></table>
PSA concentration: Median (Interquartile range)
I: 209 (66-678); C: 158 (42-548)

Time from diagnosis (years): Median (Interquartile range)
I: 3.0 (1.6-5.1); C: 2.9 (1.5-4.6)

Previous treatments:
Hormonal therapy (some patients continued on dual therapy)
<table><tr><td>Therapy</td><td>I: n (%)</td><td>C: n (%)</td></tr><tr><td>Orchidectomy</td><td>46 (57)</td><td>47 (58)</td></tr><tr><td>Estrogen</td><td>7 (9)</td><td>11 (14)</td></tr><tr><td>LHRH</td><td>15 (19)</td><td>8 (10)</td></tr><tr><td>Cyproterone acetate</td><td>20 (25)</td><td>17 (21)</td></tr><tr><td>Flutamide</td><td>24 (30)</td><td>9 (11)</td></tr></table>
Median age of participants:
I(1): 69; C: 67.

Age IQ range of participants:
I(1): 63-75; C: 64-74</td>
<td>Intervention: Mitoxantrone + Prednisone
No. randomised: 80
Route of administration: mitoxantrone: i.v.; prednisone: p.o.
Dose: mitoxantrone 12 mg/m2 every 3 wks; prednisone 5 mg b.i.d.

If nadir blood cell counts showed granulocytes < 0.5 x 10^9/L or platelets < 50 x 10^9/L then mitoxantrone dose was reduced by 2 mg/m2 on subsequent cycles.
If nadir blood cell counts showed granulocytes> 1.0 x 10^9/L and platelets > 100 x 10^9/L with minimal non-haematologic toxicity then dose was increased by 2 mg/m2 on subsequent cycles.

No. of cycles: until cumulative dose of 140 mg/m2 reached, with dose reductions as above.
Length per cycle: 3 weeks if serum concentrations were above the following values:
WBC > 3 x 10^9/L
Granulocyte > 1.5 x 10^9/L
Platelet > 100 x 10^9/L
If values were lower treatment was delayed until levels were exceeded.

Control: Prednisone

No. randomised: 81</td>
<td>Outcome 1: Overall Survival (N=161)
No significant difference in overall survival;140 total deaths (P = 0.27, favouring I group)

From Moore et al. (1996)[49]:
Median survival was 10 months, with no difference between I and C (P=0.15, favouring I).

Univariate regression analysis for time to death (from Dowling et al. (2001)[45]):
<table><tr><td>Variable</td><td>P</td><td>HR (95% CI)</td></tr><tr><td>Older age</td><td>0.26</td><td>1.01 (0.99, 1.03)</td></tr><tr><td>Increasing ECOG</td><td>< 0.0001</td><td>1.6 (1.29, 1.99)</td></tr><tr><td>Increasing pain</td><td>< 0.0001</td><td>1.59 (1.3, 1.94)</td></tr><tr><td>Increasing haemoglobin</td><td>< 0.0001</td><td>0.98 (0.97, 0.99)</td></tr><tr><td>Increasing alkaline phosphatase</td><td>0.003</td><td>1 (1,1.001)</td></tr><tr><td>Increasing PSA</td><td>0.93</td><td>1 (1,1)</td></tr><tr><td>PSA response</td><td>0.0004</td><td>0.47 (0.31, 0.72)</td></tr><tr><td>Palliative response</td><td>0.055</td><td>0.71 (0.5, 1.01)</td></tr></table>
Multivariate analysis of baseline factors & PSA response (from Dowling et al. (2001)[45]):
<table><tr><td>Variable</td><td>P</td><td>OR (95% CI)</td></tr><tr><td>Older age</td><td>0.13</td><td>1.02 (0.99, 1.05)</td></tr><tr><td>Increasing ECOG</td><td>0.005</td><td>1.53 (1.14, 2.07)</td></tr><tr><td>Increasing pain</td><td>0.05</td><td>1.32 (1.001, 1.75)</td></tr><tr><td>Increasing haemoglobin</td><td>0.003</td><td>0.98 (0.97, 0.99)</td></tr><tr><td>Increasing alkaline phosphatase</td><td>0.14</td><td>1 (1, 1.001)</td></tr><tr><td>PSA response</td><td><0.0001</td><td>0.35 (0.22, 0.56)</td></tr></table></td>
<td>Authors' conclusions: Chemotherapy with mitoxantrone plus prednisone provides palliation for some patients with symptomatic hormone-resistant prostate cancer.

Comments: Supported by Lederle laboratories, Division of Cyanamid Canada inc.

An independent external consultant (from National cancer Institute of Canada) reviewed records of all responding patients and a randomly selected series of additional patients.

There were some inconsistencies between the original trial publication and the FDA report; for example the number of crossovers differ. Where this occurred, the data from the trial publication were used.</td>
</tr>
</table>

Method of randomisation:
-Assignment/Allocation:
Not reported (stratified by ECOG score: 0,1 vs 2,3).

ITT analysis performed: Yes

Per protocol analysis performed: Not Stated

Comments: .Power calculations required a sample size of 150. For PSA sensitivity analysis patients with missing data are considered non-responders (From Dowling et al. (2001)[45])

Baseline comparability: Trend for patients randomised to I to have a higher analgesic score & to be treated with flutamide.

Eligibility criteria specified: Yes

Co-interventions: Patients continued analgesic medication and primary anti-androgen therapy. Additional anti-androgen therapy was discontinued by most patients. Prochlorperazine recommended as anti-emetic; Dexamethasone or other steroids not used.

Blinding:
- **Outcome assessor:** Not reported
- **Carer:** Not reported

Other participant characteristics:
ECOG Performance status:

status	I: n (%)	C: n (%)
0	5 (6)	3 (4)
1	45 (57)	47 (59)
2	21 (26)	22 (28)
3	8 (10)	8 (10)
Unknown	1 (1)	1 (1)

Present pain intensity

score	I: n (%)	C: n (%)
0	1 (1)	1 (1)
1	30 (38)	23 (28)
2	30 (38)	37 (46)
3	15 (19)	15 (19)
4	4 (5)	5 (6)

Analgesic score: Median (Interquartile range)
I: 18 (10-30); C: 14 (6-24)

Overall QoL (LASA scale; 0=extremely ill-10=feel well): Median (Interquartile range)
I: 5.9 (4.7 -8.1); C: 6.5 (4.8-8.0)

Overall QoL (EORTC QLQ-C30; 0=very poor-100=excellent): Median (Interquartile range)
I: 46 (33-58); C: 50 (33-58)

Comments about participants:

Inclusion/exclusion criteria: Metastatic adenocarcinoma of the prostate, with symptoms that included pain and disease progression despite standard hormonal therapy.
ECOG score ≥ 3.
Life expectancy ≥ 3 months and capable of completing pain & QoL scales.
Serum concentrations of WBC > 3.0 x 10^9/L; polymorphonuclear granulocytes

Route of administration: p.o.
Dose: 5 mg b.i.d.
No. of cycles:
Length per cycle:

Comments about control group: Nonresponding patients or those with progressive symptoms after treatment for ≥ 6 wks were crossed over I;. 50 (62%) patients crossed over- *this was reported as 48 elsewhere*.

Median time of crossover was at 84 days (range: 11- 324 days)

Patients still responding after a cumulative dose of 140 mg/m2 mitoxantrone were crossed over to C to minimise probability of cardiac toxicity.

Protocol deviations:
Halfway through study withdrawal responses to flutamide were recognised; patients then evaluated for ≥ 4 wks after stopping flutamide before entry into study.
3 patients crossed over from C to I before 6 wks due to rapid progression.

Multivariate analysis of baseline factors and palliative response (from Dowling et al. (2001)[45]):

Variable	P	OR (95% CI)
Older age	0.07	1.02 (0.99, 1.05)
Increasing ECOG	0.005	1.44 (1.12, 1.85)
Increasing pain	0.0008	1.46 (1.17, 1.81)
Increasing haemoglobin	0.02	0.99 (0.98, 0.99)
Increasing alkaline phosphatase	0.07	1 (1,1)
Palliative response	0.11	0.74 (0.51, 1.07)

Outcome 2: Progression-free survival
From Center for Drug Evaluation and Research (1996)[20]
(response based on primary criterion only)

Responders (N=33):
I: n=23; C: n=10
Median time to progression (N=147):
I: 301 days; C: 133 days P=0.0001
(relationship remained when controlling for baseline performance status and PPI score).

Non-responders (N=128, data available for 114)
I: n=54; C: n= 60
Median time to progression:
I: 70 days; C: 54 days P=0.0116

All Patients (N=147)
I: n=77; C: n= 70
Treatment failures:
I: 43; C: 60
Median time to progression:
I: 148 days; C: 62 days P=0.0001

Outcome 3: Response Rate
Palliative response, *primary outcome of paper* (defined as 2 point reduction in the PPI scale, or complete relief if 1+ initially, without an increase in analgesic score maintained on 2 consecutive visits at least 3 weeks apart) (N=161):
I: 23/80 (29%; 95% CI: 19%, 40%)
C: 10/81 (12%: 95% CI: 6%, 22%)
(P = 0.01)

<table>
<tr>
<td>- Patient: Not reported
- Success assessed: Not reported

80% Follow-up: Yes</td>
<td>> 1.5 x 10^9/L; platelets > 150 x 10^9/L; bilirubin < 54 µmol/L; testosterone < 3.5 nmol/L.
Exclusion criteria were: prior malignancy except non-melanotic skin cancer; prior chemotherapy or treatment of cancer with glucocorticoids; treatment with radiotherapy in the previous month or strontium 89 in the previous 2 months; contraindictions to the use of prednisone – e.g. peptic ulcer; uncontrolled cardiac failure or active infection.</td>
<td></td>
<td>Response duration (mean):
I: 43 weeks
C: 18 weeks
(P < 0.0001)

11/50 (22%) patients responded to M+P on crossover for median duration 18 weeks (range 9-69).

Palliative response – secondary criteria (≥50% reduction in analgesic score without an increase in pain on 2 consecutive visits at least 3 weeks apart)
I: 7 patients in addition to those meeting primary
C: 7 as above

Response duration (mean)
I: 33 weeks
C: 24 weeks

Primary plus secondary response:
I: 30/80 (38%)
C: 17/81 (21%)
(P = 0.025)

Univariate regression analysis (from Dowling et al. (2001)[45])
<table>
<tr><th>Variable</th><th>P</th><th>OR (95% CI)</th></tr>
<tr><td>Older age</td><td>0.53</td><td>1.02 (0.97,1.06)</td></tr>
<tr><td>Increasing ECOG</td><td>0.01</td><td>0.53 (0.31, 0.91)</td></tr>
<tr><td>Increasing pain</td><td>0.10</td><td>0.72 (0.48, 1.07)</td></tr>
<tr><td>Increasing haemoglobin</td><td>0.03</td><td>1.02 (1, 1.05)</td></tr>
<tr><td>Increasing alkaline phosphatase</td><td>0.04</td><td>1 (0.99,1)</td></tr>
<tr><td>Increasing PSA</td><td>0.38</td><td>1 (1,1)</td></tr>
</table>
Outcome 4: PSA Decline
PSA response (maximum observed decrease; ≥25% includes those with ≥50% or ≥75; ≥50% includes those with ≥75%)

Assessment at baseline & 1 subsequent visit for 111 patients.
<table>
<tr><th>Decrease</th><th>I: n (%)</th><th>C: n (%)</th></tr>
<tr><td>≥ 25%</td><td>28 (49)</td><td>25 (46)</td></tr>
<tr><td>≥ 50%</td><td>19 (33)</td><td>12 (22)</td></tr>
<tr><td>≥ 75%</td><td>13 (23)</td><td>5 (9)</td></tr>
</table>
(P = 0.11)</td>
<td></td>
</tr>
</table>

Sensitivity analysis effect of PSA response on palliative response (From Dowling et al. (2001)[45]):

PSA response	Palliative response		No palliative response	
	I	C	I	C
≥50%	18	1	9	8
Stable	9	9	17	14
Primary non-responder	2	6	13	20
Unevaluable	1	1	11	22

P = 0.001

Outcome 5: Adverse events
Assessed by WHO criteria.
Minimal toxicity attributable to prednisone. Toxicity attributable to mitoxantrone, including patients crossed over to this treatment (total = 130 patients; 796 courses):

Hematologic toxicity:

Granulocyte nadir x 10^9/L:
0.5-1.0: 171 courses (32%)
< 0.5: 69 courses (13%)
Neutropenia (< 1.0 x 10^9/L) with sepsis: 9 courses (1.1%)
Platelet nadir x 10^9/L
50-100: 22 courses (4.2%)
< 50: 3 (0.6%)

Cardiac toxicity: 5 patients experienced cardiac toxicity measured by lower than normal left ventricular ejection fraction (<50%). 3 were asymptomatic, 2 had congestive heart failure, 1 also had atrial fibrillation.

Nausea and vomiting: assessed for 654 cycles in 120 patients (including crossover).
None: 71% cycles
WHO grade 3-4: 3 cycles (0.5%)

Alopecia:
None: 90 (76%)
Remainder: minimal/patchy loss

Outcome 6: Pain
Pain measured on 3 scales (N=138)
Data from Stockler et al. (1998)[48]

			Differences between I and C (all favour I) in measures of pain: median (95% CI) LASAS: 11 (2-20) P = 0.014 QLQ-C30: 8 (0-17) P = 0.027 PPI: 0 (0-20) P = 0.088 Mean (95% CI) LASAS: 13 (3-22) P = 0.010 QLQ-C30: 11 (2-20) P = 0.023 PPI: 8 (1-15) P = 0.030 **Outcome 7: Health related QoL** Pain intensity scales completed for 92% clinic visits during initial treatment, LASA scales for pain on 89% visits. 78 patients in I assessed; 76 in C (N=154). Scales with significant differences Pain LASA median changes (P = 0.01) LASA best changes (P = 0.01) EORTC median changes (P < 0.05) EORTC best changes (P < 0.05) Constipation LASA median changes (P < 0.05) LASA best changes (P < 0.05) EORTC best changes (P < 0.05) Mood LASA best changes (P = 0.02) Data from Osoba et al. (1999)[46] Data given for 3 groups – I, C after 6 wks and x-over from C to I after 6 weeks. I: (n = 71) improvements compared with baseline in physical functioning, social functioning, global QoL, pain, anorexia, constipation, impact of pain on mobility, degree of pain relief, drowsiness (0.0001 < P < 0.009). Increased alopecia was only significant negative effect (P = 0.009). After 4 cycles (n = 54) continued improvement in 4 functioning scores (0.0001 < P < 0.004), global QoL (P = 0.009) & 9 symptoms (0.0001 < P < 0.01), alopecia showed continued deterioration (P = 0.001)	

			After 6 cycles (n = 43) showed continued improvement in 11 of 14 scales showing improvement after 4 cycles. Duration of improvements ranged from 11 to 19 weeks C: (n = 62) improvements compared with baseline in social functioning, global QoL, nausea & vomiting, anorexia (0.003 < P < 0.007) and impact of pain on mobility (P = 0.01). After 4 cycles (n = 42) no measure showed significant difference from baseline After 6 cycles (n = 19) only impact of pain on mobility was better than baseline (P = 0.004) Duration of improvements ranged from 3 to 7 weeks x-over group (n = 35) after 6 weeks (2 cycles) of I had improvements in pain, insomnia & impact of pain on mobility (0.0001 < P < 0.01) after 4 cycles (n = 25) there was improved global QoL (P = 0.003) and pain relief (P = 0.0001) After 6 cycles (n = 17) improved pain, impact of pain on mobility & pain relief (0.001 < P < 0.003), but greater alopecia (P = 0.01). Duration of improvement ranged from 4 to 26 weeks Duration of improvement > 10 points was longer in I than C in social functioning, pain, impact of pain on mobility, pain relief, insomnia & drowsiness (0.004 < P < 0.048). Duration of improvement > 10 points was longer in x-over than C in pain, pain relief and drowsiness. **Discontinuations:** 1 diabetic patient in control group discontinued treatment due to toxicity. Number of cycles of I received: Median (range): 6.5 (1-18) Dose of I received: Median (range): 12 mg/m^2 (5.1 mg/m^2-16.5 mg/m^2) Mitoxantrone therapy was delayed for one or more cycles in 7 (9%) of patients originally in I group.	

Study Details and Design	Participant Details	Intervention Details	Results	Conclusion and Comments
Author: Kantoff et al. (1999)[32] **Country:** USA **Primary source:** Embase **Aim:** To demonstrate an advantage of mitoxantrone and hydrocortisone over hydrocortisone alone with respect to survival duration. **Trial ID:** CALGB 9182 **Phase:** III **Length of follow-up:** 2-year follow up after the accrual period (which lasted 3 years). **Number and times of follow-up measurements:** Serum PSA measurements every 3 weeks, bone scan every 2 months for the first 4 months, then every 3 months thereafter. Other scans were performed in the presence of measurable disease every 2 months. QOL assessments at study entry, 6 weeks, 12 weeks then 12 week intervals thereafter, until final assessment at treatment failure. Quality of Life assessments used were Functional Living Index-Cancer (FLIC), Symptom distress Scale, Sexual and urologic functioning scale, problems in daily activities	**Number randomised:** 242, 238 eligible. **Disease characteristics:** Metastases: | | I:% | C:% | | Bone | 91 | 90 | | Lymph node | 21 | 17 | | Lung | 9 | 9 | | Liver | 9 | 16 | Patients may have > 1 metastasis Years since diagnosis, median: I: 3.3 (IQ range:1.9-6.3) C: 3.4 (IQ range: 1.9-5.2) PSA, median: I: 150 ng/mL (IQ range: 52-362) C: 141 ng/mL (IQ range: 54-416) **Previous treatments:** | | I:% | C:% | | Surgical castration | 59 | 61 | | Estrogen | 8 | 13 | | LHRH analog | 47 | 45 | | Progesterone agent | 7 | 18 | | Antiandrogen | 69 | 75 | Patients may have > 1 prior therapy. **Median Age of participants:** 72 **Age range of participants:** (IQ range) I: 67-75; C: 65-75 **Other participant characteristics:** QOL, performance status 0-1: I: 85%; C: 88% QOL, no analgesic use:	**Intervention:** Hydrocortisone + Mitoxantrone **No. randomised**: 119 **Route of administration:** Hydrocortisone: p.o.; mitoxantrone: i.v. **Dose:** Hydrocortisone b.i.d. (30 mg in morning, 10 mg in evening); mitoxantrone 14 mg/m2 every 3 weeks. **No. of cycles:** **Length per cycle:** 3 weeks **Control:** Hydrocortisone **No. randomised:** 123 **Route of administration:** p.o. **Dose:** Hydrocortisone b.i.d. (30 mg in morning, 10 mg in evening). **No. of cycles:** **Length per cycle:** 3 weeks. **Comments about intervention/control:** dose modifications permitted in the presence of hematopoietic toxicity. No crossovers permitted, although alternative chemotherapy regimes allowed after disease progression. Hydrocortisone continued in all patients, until disease progression or treatment failure (encouraged until death).	**Outcome 1: Overall survival** *(primary outcome of trial).* Median survival: I:12.3 months; C:12.6 months; log-rank test=0.08, df=1, P=0.77. Adjusted HR:1.0 (95% CI: 0.8-1.3, P=0.976) From Center for Drug Evaluation and Research (1996)[20]: Number of deaths: I: 58/119 C: 68/123 **Outcome 2: Progression-free survival** Time to disease progression (defined as worsening performance status of ≥1 or the appearance of 2 or more new lesions on bone scan, or an increase in serum PSA ≥100% from baseline). Small but statistically significant difference favouring I group with respect to time to disease progression. (p=0.0218) From Center for Drug Evaluation and Research (1996)[20]: Numbers progressed: I: 56; C: 71 (p=0.0654) Progressed according to measurable disease criteria: I: 29 (31%); C: 28 (27%) Progressed according to bone scan: I:66 (69%); C:77 (71%) Progressed according to PSA: I: 54 (57%); C: 48 (46%) Progressed according to performance status: I: 38 (39%); C: 42 (39%) Time to treatment failure (defined as disease progression, appearance of unacceptable toxicity, or patient refusal of therapy). Small but statistically significant difference favouring I group with respect to time to treatment failure (data not shown). Time to Treatment failure and disease progression (median): I:3.7 months; C: 2.3 months. P=0.025 for treatment failure. P=0.022 for disease progression. **Outcome 3: Response rate N=234** Best response (in either measurable disease, assessable disease, or bone-	**Authors' conclusions:** I generated more frequent responses and delayed time to treatment failure and disease progression, compared to C. Possible benefit of intervention with respect to pain, although no improvement in survival was observed. **Comments:** CALGB data management centre personnel were responsible for quality assurance of all data. Supported in part by Immunex through a grant to the Cancer and Leukaemia Group B. There were some inconsistencies between the original trial publication and the FDA report; for example the p-value for progression – free survival differ. Where this occurred, the data from the trial publication were used.

scale, impact of pain on daily activities instrument. **Method of randomisation:** **-Assignment:** stratified by performance status (0-1 v 2) and disease status (measurable v assessable). After first 60 patients were accrued, patients were then stratified by number of prior endocrine manipulations (1 v ≥ 2) **-Allocation:** Not stated **ITT analysis performed:** 1 in intervention, 3 in control ruled ineligible, but included in survival analysis. Response rate data included 234 eligible patients who started treatment. **Per protocol analysis performed:** Not stated **Comments:** Sample size calculations indicated a sample size of 232 was required. **Baseline comparability:** C group tended to have had more prior treatments with a progestational agent. **Eligibility criteria specified:** Yes **Co-interventions:** Continuation of LHRH for those who had not undergone an orchiectomy. Use of growth factors discouraged.	I: 35%; C:40% White race: I: 88%; C: 93% **Comments about participants:** **Inclusion/exclusion criteria:** Patients with metastatic prostate cancer, who had undergone no more than 1 prior endocrine manipulation (however this criteria was removed after accrual of 60 patients). Patients were required to have adequate hepatic, renal and bone marrow function. Antiandrogen withdrawal and documented disease progression were required before trial entry.	From Center for Drug Evaluation and Research (1996)[20]: Maximum cumulative dose of mitoxantrone was 160 mg/m^2. **Protocol deviations:** 2 in each treatment arm never started treatment.	only disease. Complete response defined as disappearance of all disease by scans, and normalisation of PSA, ≤4 ng/mL, sustained for ≥28 days. Partial response for measurable disease was defined as ≥50% reduction in bidimensional measurable disease for ≥4 weeks, or a partial response for any of the 3 categories was a ≥ 80% reduction in PSA for ≥6 weeks) (see also PSA decline) No complete responses were observed. Partial responses: I:8 (7%); C:5 (4%) No significant difference (P=0.375) Stable disease: I:65/116 (56%); C:5/118 (42%) Post hoc analysis, number of patients with complete response, partial response or stable disease: I: 73/116 (64%); C: 55/118 (47%) P=0.012 **Outcome 4: PSA Decline N=228** Defined as ≥50% or ≥80% reduction in serum PSA from baseline at between 4 and 8 weeks of follow-up: PSA response | I: n(%) | C: n(%) <50% | 78 (81.3) | 78 (85.7) ≥50%* | 18 (18.7) | 13 (14.3) ≥80%* | 4 (4.2) | 4 (4.3) *Not mutually exclusive. No significant differences Post-hoc (all trial): PSA response | I: n(%) | C: n(%) <50% | 70 (62.5) | 91 (78.5) ≥50%*⊥ | 42 (37.5) | 25 (21.5) ≥80%*┼ | 22 (19.6) | 11 (9.5) * not mutually exclusive. ⊥P=0.008 ┼P=0.029 Survival curve by PSA reduction available; median survival: ≥50% or ≥80% reduction: 20.5 months <50% reduction: 10.2 months (P<0.001) **Outcome 5: Adverse events** Grade 3 and 4 specific toxicities were reported for 206 (86%) of patients.	

Blinding:
- **Outcome assessor:** No
- **Carer:** No
- **Patient:** No
- **Success assessed:** N/A

80% Follow-up: Yes

Grade 3 or 4 haematopoietic adverse events.

	I: % (n/N)	C: % (n/N)
WBC*	59 (66/112)	1 (1/113)
Platelets⊥	6 (7/112)	0 (0/112)
Granulocytes/ bands*	63 (71/112)	1 (1/113)
Lymphocytes*	70 (77/110)	15 (17/111)
Cardiac	5	0

No reported treatment related deaths.
*P<0.001 ⊥P<0.01

Outcome 6: Pain
Not reported.

Outcome 7: Health related QoL
196 (84%) completed at least 1 of 5 QOL instruments at baseline, 183 (78%) completed at least 1 instrument after baseline. 155 (66%) were assessed at baseline and at least 1 follow-up.

51 who did not have post-baseline QoL assessments tended to have a poorer performance status and lower QOL at baseline.

	Difference	p-value
FLIC: total	-4.34	0.12
Symptom distress: total	0.05	0.96
Sexual & urologic function: total	0.08	0.89
Probs in daily life	-1.25	0.20
Impact of pain	-1.87	0.38
FLIC: physical well–being	-1.90	0.29
FLIC: emotional state	-1.42	0.04
FLIC: family disruption	-0.93	0.02
FLIC: pain from cancer	0.35	0.26
FLIC: pain interferes	-0.18	0.43
Symptom distress: pain, how often	-0.30	0.06
Symptom distress: pain, how severe	-0.28	0.03
Symptom distress: appetite	0.08	0.59
Symptom distress: fatigue	-0.06	0.68

-ve favour I, +ve favour C.

Discontinuations: Not reported

Number of cycles: Median of 5 cycles of mitoxantrone.

<table>
<tr><th>Study Details and Design</th><th>Participant Details</th><th>Intervention Details</th><th>Results</th><th>Conclusion and Comments</th></tr>
<tr>
<td>Author: Ernst et al. (2003)[33]

Country: Canada

Primary source: Medline

Aim: To compare the incidence of palliative response in patients with HRPC treated with mitoxantrone plus prednisone (MP) plus clodronate with that of patients treated with MP and placebo.

Trial ID:

Phase: III

Length of follow-up: Not stated
Median: Not stated

Number and times of follow-up measurements: All patients were reviewed every 3 weeks, completing the present pain intensity scale (PPI) and health-related quality of life (HRQOL) questionnaires (using the Prostate cancer-specific Quality of Life Instrument (PROSQOLI)), undergoing toxicity assessment using the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) Expanded Toxicity Criteria, and PSA levels were measured at each visit.</td>
<td>Number randomised: 227, 209 included in analysis

Disease characteristics:
ECOG performance status:
<table>
<tr><th></th><th>I: n (%)</th><th>C: n (%)</th></tr>
<tr><td>0</td><td>9 (9)</td><td>14 (13)</td></tr>
<tr><td>1</td><td>60 (58)</td><td>65 (62)</td></tr>
<tr><td>2</td><td>30 (29)</td><td>21 (20)</td></tr>
<tr><td>3</td><td>5 (5)</td><td>5 (5)</td></tr>
</table>
PPI:
<table>
<tr><th></th><th>I: n (%)</th><th>C: n (%)</th></tr>
<tr><td>Mild (PPI:1,2)</td><td>78 (75)</td><td>82 (78)</td></tr>
<tr><td>Moderate (PPI: 3,4)</td><td>26 (25)</td><td>23 (22)</td></tr>
</table>
PSA at study entry:
I: median: 128.5 (IQ range: 47.9 – 394.8 ng/ml)
C: median: 150.4 (IQ range: 45.5 – 361 ng/ml)

Daily morphine equivalents, mg:
I: median=70 (IQ range: 40-114)
C: median=57 (IQ range: 28.5-107)

Previous corticosteroids:
I: Yes=13 (13%); No=91 (88%)
C: Yes=9 (9%); No=96 (91%)

Median age of participants:
I(1): 70.1; C: 70.6.
Age IQ range of participants:
I(1): 65.4-76.4; C: 64.4-74.6

Other participant characteristics:

Comments about participants:

Inclusion/exclusion criteria:</td>
<td>Intervention:
Mitoxantrone + prednisone + clodronate

No. randomised: 115 (11 ineligible)
Route of administration: Mitoxantrone and clodronate: i.v.
Dose: mitoxantrone: 12 mg/m2 every 3 weeks; prednisone 5 mg b.i.d.;clodronate: 1,500 mg over 3 hours.
No. of cycles: Mitoxantrone discontinued after cumulative dose of 140 mg/m2. In patients with a palliative response, other study drugs given until disease progression. Clodronate was withheld if serum calcium <2.01mmol/L or serum creatinine >200nmol/L.
Length per cycle: 3 weeks

Control: Mitoxantrone + prednisone + placebo.

No. randomised: 112 (7 ineligible)
Route of administration: Mitoxantrone and placebo: i.v.
Dose: mitoxantrone: 12 mg/m2 every 3 weeks; prednisone 5 mg b.i.d.; placebo: 1,500 mg normal saline over 3 hours.
No. of cycles: Mitoxantrone discontinued</td>
<td>Outcome 1: Overall survival
Deaths (N=176): I=87;C=89

Median survival:
I:10.8 months (95% CI:8.2-13.0)
C:11.5 months (95% CI: 8.8-14.4)
HR (C/I): 0.95 (95% CI: 0.71-1.28)

Adjusted HR (I/C):1.05 (95% CI: 0.78-1.43)

Adjusted HR (haemoglobin ≥100 g/L vs < 100 g/L): 0.52 (95%CI: 0.35-0.78, P=0.001)

Outcome 2: Progression-free survival Symptomatic progression free survival (SPFS), (defined as time from randomisation to date of progression (pain or other symptoms), for those who died without progression, date of death was used).

Developed progression:
I= 95; C=101

Median SPFS:
I:5.0 months (95% CI:4.1-6.8)
C:4.0 months (95% CI: 2.9-4.9)
HR (C/I):1.237 (95% CI: 0.934-1.64)

Adjusted HR(I/C):0.76 (95% CI: 0.57-1.02, P=0.07)

Adjusted HR (haemoglobin ≥100 g/L vs < 100 g/L): 0.67 (95%CI: 0.46-0.99, P=0.043)

Outcome 3: Response Rate
Palliative response (defined as either a 2-point reduction in PPI and without an increase in analgesic score or evidence of disease progression, or > 50% decrease in analgesic score without an increase in PPI, on 2 consecutive evaluations at least 3 weeks apart) (N=209): (primary outcome of paper)

I: 46/104 (45%)
C: 41/105 (39%)
No significant difference (P=0.54, and P=0.37 when controlling for stratification variables).</td>
<td>Authors' conclusions: Mitoxantrone plus prednisone provide palliation in symptomatic sufferers of HRPC. Clodronate does not increase palliative response rate or overall QOL-may be more beneficial for those with moderate pain, but this requires further confirmation.

Comments: Supported by Immunex and Aventis.</td>
</tr>
</table>

Repeat radiological studies were only performed when clinically indicated, and calcium, creatinine and pyridinium cross-links were tested every 12 weeks using urine samples. A daily pain diary was also maintained. **Method of randomisation**: -**Assignment**: Block-randomisation. Stratified by pain level (mild = PPI 1 or 2, moderate = PPI 3 or 4) and previous corticosteroid use (yes or no). -**Allocation:** Not reported. **ITT analysis performed**: 18 patients randomised and ineligible at baseline, 209 analysed on ITT basis for pre-treatment characteristics, response rates, survival, time to progression and HRQOL. **Per protocol analysis performed**: Safety and drug exposure analyses based on actual drug received. **Comments**: power calculations required sample size of 204. **Baseline comparability:** Trend toward better ECOG performance status and lower daily morphine equivalents in control group. **Eligibility criteria specified**: Yes. **Co-interventions**:	Histologically confirmed adenocarcinoma of the prostate or metastatic carcinoma (presumptive prostate origin), defined by the presence of sclerotic bony metastases and a serum PSA > upper limit of normal. Radiologically confirmed, progressive bone disease (defined as presence of new lesions on bone scan, increased isotope uptake at previous sites of disease, or increasing bone pain). Castrate levels of testosterone (<3 nmol/L), withdrawal of nonsteroidal antiandrogens a minimum of 4 weeks (flutamide, nilutamide) or 6 weeks (bicalutamide) before randomisation required. No radiotherapy within the previous 4 weeks, or radioisotopes within the previous 8 weeks. PPI ≥ 1 required (based on the average pain level for the last 24 hours). Stable analgesic use (measured by the use of an analgesic diary, with scores of 1 for standard doses of nonopioids, and 2 for opoid doses of morphine 10 mg equivalents), stable was defined as no more than 25% variance in analgesic scores in the week before randomisation. ECOG score < 3 and baseline measurement of LVEF > 50% and ability to complete pain and QoL forms required. Laboratory criteria were WBC ≥3.0 x 10^9/L, absolute granulocyte count ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L, bilirubin ≤ 54 nmol/L, serum calcium ≤3.10 mmol/L, serum creatinine < 200 nmol/L. Exclusion criteria were: prior malignancy (excluding nonmelanoma skin cancer), >1 previous chemotherapy regimen, or 1 containing mitoxantrone or an anthracycline, previous	after cumulative dose of 140 mg/m2. In patients with a palliative response, other study drugs given until disease progression. Placebo was withheld if serum calcium <2.01mmol/L or serum creatinine >200nmol/L. **Length per cycle:** 3 weeks **Comments about intervention/control**: mitoxantrone discontinued if 2 consecutive delays of 1 week for neutropenia or thrombocytopenia occurred. Dose reduction to 9 mg/m2 if neutropenic fever or bleeding associated with platelet count <100x10^9/L present. Disease progression was defined as 1 or more of the following: ≥ 1 point increase in the PPI, 25% increase in analgesic consumption, need for palliative radiotherapy, or unequivocal evidence of radiological progression. **Protocol deviations:** 1 patient randomised to clodronate arm received placebo. Reason for discontinuation of protocol treatment was protocol violation for 14/104 patients in I group and 10/104 patients in C group.	No difference when included all randomised (N=227): I: 49/115 (43%) C: 42/112 (37.5%) (P=0.52) Subgroup-baseline PPI score: Mild pain (PPI 1,2): OR=0.9 (95% CI:0.5 – 1.7) Moderate pain (PPI 3,4): I: 58% (95% CI: 41%-77%) C: 26% (95% CI: 13%-48%) OR= 4.6 (95% CI:1.3-15.5, P=0.04) Duration of palliative response (time from first date at which palliative response criteria fulfilled to first date at which disease progression was noted): I: median=6.2 months (95% CI: 5.0-9.2) C:median=6.4 months (95% CI: 4.0-9.6) No significant difference (P=0.79) **Outcome 4: PSA Decline** (50% or more decrease in serum PSA compared to baseline for at least 2 visits) (N=209): I: 30 (29.7%) C: 30 (28.6%) **Outcome 5: Adverse events** Drug-related toxicities at grade 3 or 4: **Outcome 6: Pain** Pain response (defined as ≥2 point reduction in PPI score in comparison with baseline, irrespective of analgesic response) (N=209): I: 34/104 (33%)	

	I: n	C: n
Granulocytopenia	14	14
Anaemia	8	5
Thrombocytopenia	2	4
Cardiovascular	0	3
Nausea/vomiting	9	7
Headache	4	1
Shortness of breath	4	7
Infection	7	3

<table>
<tr>
<td>Prochlorperazine or metoclopramide were recommended as antiemetics. Dexamethasone or other corticosteroids were not allowed. Continuation of hormonal therapy allowed, additional androgen ablation not permitted. Patients received analgesics during the study.

Blinding:
- Outcome assessor: Not stated.
- Carer: Yes.
- Patient: Yes.
- Success assessed: Not stated.

80% Follow-up: Yes.</td>
<td>bisphosphonate therapy, radicular or back pain (suggestive of epidural metastases), spinal cord or nerve root compression, impending pathologic fracture, uncontrolled cardiac failure or active infection.</td>
<td></td>
<td>C: 27/105 (26%)
No significant difference (P=0.34)

Analgesic response (defined as 50% decrease in analgesic score from baseline with no increase in pain):
I: 34/104 (33%)
C: 32/105 (30%)
No significant difference (P=0.84)

Numbers of patients who no longer required analgesics for 2 consecutive cycles:
I: 33/104 (31%)
C: 27/105 (25%)
No significant difference (P=0.42)

Outcome 7:Health related QoL
HRQOL response (defined as 1 cm improvement on the 10 cm visual analogue scale, maintained on 2 consecutive visits, no less than 3 weeks apart).

Response rate (N=209):
I: 39 (37.5%); C: 44 (42%)
No significant difference.

Discontinuations:
<table>
<tr><td>Reason</td><td>I: n (%)</td><td>C: n (%)</td></tr>
<tr><td>Progressive disease, overall</td><td>58 (56)</td><td>68 (65.4)</td></tr>
<tr><td>Development of new lesions</td><td>15 (14)</td><td>24 (23)</td></tr>
<tr><td>Radiologic progression</td><td>18 (17)</td><td>14 (13)</td></tr>
<tr><td>Requirement of local radiotherapy</td><td>18 (17)</td><td>16 (15)</td></tr>
<tr><td>Death</td><td>5 (4.5)</td><td>3 (2.9)</td></tr>
<tr><td>Toxicity</td><td>3 (2.9)</td><td>2 (1.9)</td></tr>
<tr><td>Patient refusal</td><td>11 (10.6)</td><td>10 (9.6)</td></tr>
<tr><td>Protocol violation</td><td>14 (13.5)</td><td>10 (9.6)</td></tr>
<tr><td>Other</td><td>13 (12.5)</td><td>11 (10.6)</td></tr>
</table>
50% I patients and 44% C patients received at least 7 cycles of therapy.</td>
<td></td>
</tr>
</table>

Appendix 10.7. Quality checklist for included trials

Quality criteria	TAX 327	Oudard et al.	SWOG 9916	Berry et al.	CCI-NOV22	CALGB 9182	Ernst et al.
Was the method used to assign participants to the treatment groups really random?	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes
What method of assignment was used?	Permuted-blocks	Not reported	Not reported	Not reported	Not reported	Not reported	Block randomisation
Was the allocation of treatment concealed?	Yes	Yes	Unclear	Unclear	No	Unclear	Unclear
What method was used to conceal treatment allocation?	Centralised	Centralised	Not reported	Not reported	N/A	Not reported	Not reported
Was the number of participants who were randomised stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were details of baseline comparability presented?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was baseline comparability achieved?	Yes	Yes	Yes	Yes	No	No	No
Were the eligibility criteria for study entry specified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were any co-interventions identified that may influence the outcomes for each group?	Yes	Yes	Yes	No	No	No	No
Were the outcome assessors blinded to the treatment allocation?	No	Not reported	Not reported	No	Not reported	No	Not reported
Were the individuals who administered the intervention blinded to the treatment allocation?	No	No	Not reported	No	Not reported	No	Yes
Were the participants who received the intervention blinded to the treatment allocation?	No	No	Not reported	No	No	No	Yes
Was the success of the blinding procedure assessed?	N/A	N/A	Not reported	N/A	Not reported	N/A	Not reported
Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the reasons for withdrawals stated?	Yes	Yes	Yes	No	Yes	No	Yes
Was an intention-to-treat analysis included?	Yes	Yes	Yes	Yes (1 patient not included)	Yes	Yes	Yes

N/A= Not Applicable

Appendix 10.8. Adjusted indirect comparisons

Using the method proposed by Bucher et al.[63] and adapted from Song et al.[62] we undertook an adjusted indirect comparison to estimate the efficacy of docetaxel plus prednisone versus prednisone alone in improving overall survival for men with HRPC. Using the adjusted indirect method means that the power of randomisation in the original studies is maintained. However this method is only valid when the magnitude of the treatment effect is consistent between the different studies being compared.

The estimate of the adjusted indirect comparison is given by:

$$T_{BC} = T_{BA} - T_{CA}$$

Where T_{BA} is the treatment effect for intervention B versus intervention A, T_{CA} is the treatment effect for intervention C versus intervention A and T_{BC} is the indirect comparison of interest; the estimate of the treatment effect of intervention B versus intervention C.

The estimate of the standard error of the estimate of the indirect treatment effect, T_{BC} is given by:

$$SE(T_{BC}) = \sqrt{SE(T_{BA})^2 + SE(T_{CA})^2}$$

Where $SE(T_{BA})$ and $SE(T_{CA})$ are the standard errors of T_{BA} and T_{CA} respectively.

Worked example: docetaxel plus prednisone versus prednisone (overall survival)

Using the adjusted method, the treatment effect (T_{BC}) of overall survival for docetaxel plus prednisone versus prednisone can be calculated using mitoxantrone plus prednisone as a common comparator between trials. In this example, we have:

Interventions:

A= mitoxantrone plus prednisone

B= docetaxel plus prednisone (3-weekly)

C= prednisone

Treatment effects:
T_{BA}= HR for death; docetaxel plus prednisone versus mitoxantrone plus prednisone
T_{CA}= HR for death; prednisone versus mitoxantrone plus prednisone

We have an estimate from TAX 327[27] of T_{BA} = 0.76 (95% CI: 0.62, 0.94). Using the random effects pooled estimate calculated in section 4.4.1 we have a HR for death = 0.99 (95% CI: 0.82, 1.20) for mitoxantrone plus prednisone versus prednisone. However in order to perform the adjusted indirect comparison, mitoxantrone plus prednisone is used as the common comparator, so this figure must be inverted to give an estimate of prednisone versus mitoxantrone plus prednisone; T_{CA}= 1.01 (95% CI: 0.83, 1.22).

In order to use the adjusted indirect comparison technique, the log hazard ratios and corresponding standard errors must be used in the calculations. The results of these calculations can then be converted back to hazard ratios and standard errors (using antilog transformations), for ease of interpretation.

Therefore, using the adjusted method and the log hazard ratios and standard errors, the treatment effect for docetaxel plus prednisone versus prednisone for overall survival is given by:

$$\ln[T_{BC}] = \ln[T_{BA}] - \ln[T_{CA}] = -0.274 - 0.01 = -0.284$$

The standard error is:

$$SE(\ln[T_{BC}]) = \sqrt{SE(\ln[T_{BA}])^2 + SE(\ln[T_{CA}])^2} = \sqrt{0.106^2 + 0.321^2} = 0.338$$

According to this estimate, the 95% CI for $\ln[T_{BC}]$ is:

$$-0.284 \pm (1.96 \times 0.338) = -0.568 \text{ to } -0.0009$$

After anti-log transformations, we have a treatment effect of overall survival for docetaxel plus prednisone versus prednisone; HR for death = 0.752 (95% CI: 0.567, 0.999).

Appendix 10.9. Details of quality assessment for economic studies

All items will be graded as either ✓yes (item adequately addressed), ✗ no (item not adequately addressed), ? unclear or not enough information, NA not applicable or NS not stated.

	Bloomfield et al		Aventis-Sanofi	
Study question	**Grade**	**Comments**	**Grade**	**Comments**
1. Costs and effects examined	✓	Cost-utility analysis	✓	
2. Alternatives compared	✓	Mitoxantrone 12 mg/m^2 (every 3 weeks) plus 5 mg prednisone twice daily 5 mg prednisone twice daily		
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	3rd party payer (e.g. provincial ministry of health, insurance company or managed care plan)	✓	NHS perspective.
Selection of alternatives				
4. All relevant alternatives are compared (including do-nothing if applicable)	✗	Other chemotherapy regimes are not evaluated	✗	No comparison with best-supportive care
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	Descriptions are given with Tannock et al (1996)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated	✗		✓	
Form of evaluation				
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	✓	Cost-utility analysis	?	No adjustment for QoL
8. If a cost-minimisation design is	**NA**		**NA**	

chosen, have equivalent outcomes been adequately demonstrated?				
Effectiveness data				
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	Single trial	✓	Effectiveness estimates derived from TAX 327
10. Effectiveness data from RCT or review of RCTs	✓	Source of effectiveness data is Tannock et al (1996). See comments there.	✓	
11. Potential biases identified (especially if data not from RCTs)	✓	Discussion of the issue of crossover between treatments. 50 patients randomised to Prednisone alone crossed over (62%)	✗	
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	**NA**	Effectiveness comes from a single study Tannock et al (1996).	**NA**	
Costs				
13. All the important and relevant resource use included	✗	Costs to patients and families, operating room costs and homecare costs were not included. Justified on the basis that they were a small proportion of total costs.	✓	
14. All the important and relevant resource use measured accurately (with methodology)	✓	Resource use collected included inpatient days, outpatient clinic visits, day care, chemotherapy, radiation therapy, hormonal therapy, outpatient drugs, diagnostic and laboratory investigations.	✗	
15. Appropriate unit costs estimated (with methodology)	✓	Costs for Ontario were applied: Admission to cancer centre – Princess	✗	

		Margaret Hospital (PMH), Toronto (using hotel method) Other admissions – Ontario case cost project Outpatient costs – Ontario Health Insurance Plan (OHIP) Laboratory tests and diagnostic imaging – OHIP Chemotherapy costs – PMH Other drug costs – Ontario drug benefit formulary Radiotherapy – PMH + OHIP physician fee Blood products – Canadian red cross Surgery staff costs - OHIP		
16. Unit costs reported separately from resource use data	✗	Some example costs detailed.	✗	
17. Productivity costs treated separately from other costs	**NA**		**NA**	
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.	✓	$ CAN 1996 plus conversion to $ US	✗	
Benefit measurement and valuation				
19. The primary outcome measure(s) for the economic evaluation are clearly stated	✓	QALY	✓	
20. Methods to value health states and other benefits are stated	✓	Rating scale with transformation via published formula to estimate utility with risk	**NA**	

21. Details of the individuals from whom valuations were obtained are given	✗		**NA**	
Decision modelling				
22. Details of any decision model used are given (e.g. decision tree, Markov model)	**NA**		**NA**	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	**NA**		**NA**	
24. All model outputs described adequately.	**NA**		**NA**	
Discounting				
25. Discount rate used for both costs and benefits	✗	Not undertaken as the median survival was less than 1 year.	✗	
26. Do discount rates accord with NHS guidance?	**NA**		✗	
Allowance for uncertainty				
Stochastic analysis of patient-level data				
27. Details of statistical tests and confidence intervals are given for stochastic data	✓	Student's t test, log transformation and non-parametric statistical tests all used to compare mean total cost and produce 95% CI. Only report Student's t test results due to similarity in results.	✗	
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves).	✓	Fieller's theorem used to calculate 95% CI for ICER	✗	
29. Sensitivity analysis used to assess	✓	One-way SA of unit costs and resource	✗	

uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).		use undertaken.		
Stochastic analysis of decision models				
30. Are all appropriate input parameters included with uncertainty?	**NA**		**NA**	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	**NA**		**NA**	
32. Are the probability distributions adequately detailed and appropriate?	**NA**		**NA**	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	**NA**		**NA**	
Deterministic analysis				
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis etc)	✓	One-way SA	✓	Univariate analysis conducted for mean survival.
35. The choice of variables for sensitivity analysis is justified	✓	Unit costs and overall level of resource use	✗	
36. The ranges over which the variables are varied are stated	✓	Inpatient and outpatient costs +/- 25%, laboratory and diagnostic costs +/- 50%, surgery costs +/- 500%. Resource use within 95% CI	✓	
Presentation of results				

37. Incremental analysis is reported using appropriate decision rules	?	Base case M+P dominates P – inappropriate calculation of negative ICER.	✓	
38. Major outcomes are presented in a disaggregated as well as aggregated form	✓		✓	
39. Applicable to the NHS setting	?	Assumptions for key cost components taken from 3 Canadian centres. It is unclear how generalisable these results are to a UK setting.	✓	

Appendix 10.10. Summary of quality of life studies considered in the economic model

Author: Bennet et al. 1997[73]

Title: A comparison of perspectives on prostate cancer: Analysis of utility assessments of patients and physicians

43 physicians (from oncology and urology), 27 patients with localised prostate cancer and 17 patients with metastatic prostate cancer assessed the quality of life of three clinical metastatic prostate cancer states. The objective was to investigate the differences between physicians and patients' values for the three prostate cancer states.

The three clinical metastatic prostate cancer states were as follows:

- A = asymptomatic or stable
- B = moderate pain and fatigue with early evidence of progressive prostate cancer or early progression
- C = severe pain and fatigue with late progressive disease or advanced prostate cancer

These three health states were each comprised from three levels of 5 health attributes: pain, mood, sexual function, bladder and bowel function, and fatigue and energy.

Patients were individually interviewed to identify the number of years of perfect health that would be preferred to 10 years with the health state associated with a particular outcome. Physicians were asked to identify the fraction of a perfectly healthy year a typical patient with metastatic prostate cancer would find equivalent to one year in a less desirable health state, both followed by death. Scores were bounded on a scale from 0.0 (death) to 1.0 (perfect health).

Results for each clinical metastatic prostate cancer state in terms of median utility scores and inter-quartile ranges for physicians and patients are presented in Table 1.

Table 1: Median utility scores for physicians and patients

	A	B	C
Physicians	0.92 (0.88-0.96)	0.83 (0.67-0.88)	0.42 (0.25-0.58)
Patients Localised disease	0.88 (0.74-0.99)	0.53 (0.38-0.78)	0.05 (0.05-0.48)
Patients Metastatic disease	0.78 (0.78-0.98)	0.58 (0.38-0.78)	0.05 (0.05-0.23)

In conclusion, the utility rankings differed between patients and physicians. Patients ranked severe metastatic disease (state C) as almost equivalent to death (median score = 0.05), while physicians ranked this state about intermediate (median score = 0.42) between perfect health and death. Similarly, for the A and B health states, physicians appeared more optimistic in their assessments than patients.

Author: Chapman et al. 1998[74]

Title: Prostate cancer patients' utilities for health states: How it looks depends on where you stand

59 prostate cancer patients (with localised or metastatic disease) were recruited to assess three hypothetical prostate cancer health states based on two approaches using time trade-off (TTO).

The health states were described in terms of 5 health attributes affected by prostate cancer: pain, mood, sexual function, bladder and bowel function, and fatigue and energy. Each attribute had three levels that were used to form three separate health state descriptions, A = high, B = moderate, C= low. In addition, patients also provided an assessment of their own current health.

The first version (personal version) of time trade-off asked each of 31 patients to imagine that their current health was described by health state A (or B or C). For the TTO exercise they were asked to choose between this particular health state for ten

years and a treatment that would restore full and perfect health, but would offer less than ten years survival.

In the second version (impersonal) of time trade-off, 28 patients were asked to imagine that they had two friends, one whose current health was described by state A (or B or C). For the TTO exercise they were asked to choose between this particular health state for ten years and a treatment that would restore full and perfect health, but would offer less than ten years survival.

Several changes were made in the instrument during its development, thus limiting the subsequent findings. 24 patients in the personal TTO were presented the health state descriptions without frequency information about the mood, sexual, bladder & bowel dysfunction. The remaining 7 patients as the patients involved in the impersonal TTO were given the final health state descriptions.

The mean scores of the personal and impersonal version of time trade-off are shown in Table 2. The results show that patients responding to the impersonal version of TTO were more likely to trade off length of life for improved quality of life compared to the same health states described in the personal version.

Table 2: Mean (SD) Time Trade off (TTO) scores and standard deviation for two versions of questionnaire

	Personal version (31 patients)	**Impersonal version (28 patients)**
Health state A	0.78 (0.30)	0.78 (0.29)
Health state B	0.72 (0.35)	0.51 (0.30)
Health state C	0.35 (0.35)	0.20 (0.26)
Current Health	0.83 (0.25)	0.71 (0.32)

Author: Chapman et al. 1999[75]

Title: A multi-attribute model of prostate cancer patients' preferences for health states

Multi-attribute utility theory (MAUT) was used to develop a model to measure patients' preferences with prostate cancer medical treatment.

57 patients were recruited, 26 with localised and 26 with metastatic prostate cancer to evaluate alternative prostate cancer health states. The health states were described in terms of 5 health attributes affected by prostate cancer: pain, mood, sexual function, bladder and bowel function, and fatigue and energy. Each attribute had three levels that were used to form three clinical health state descriptions, A = high, B = moderate, C= low. A fourth personalised health state description (P) was used to match the patient's current health.

Each attribute was weighted by their relative importance, and pain received the highest attribute weight (29% of the overall value of quality of life) the other attributes received different weights among localized and metastatic prostate cancer patients.

In order to measure patients' preferences, Chapman used a time trade off (TTO) approach in order to elicit valuations for the three health states (A, B and C) and for the patient's current health state (P).

The TTO for the patients' own health state (P) was standardised by comparing it to TTO judgements for states A and C.

$$P_{stand} = P - C / A - C$$

Several changes were made in the instrument during its development; thus 22 patients were presented the TTO questions in a personal choice format, the remaining 35 patients were given an impersonal TTO description that described a hypothetical health state that would be experienced by a friend.

The mean TTO scores are shown in Table 3. The scores for states A, B, C, and P were calculated by taking the number of years in perfect health equivalent to 10 years in each health state and dividing by 10.

Table 3: Mean (standard deviation) TTO scores (N= 57)

Health state description	TTO score
State A	0.84 (0.19)
State B	0.66 (0.29)
State C	0.23 (0.25)
Personalised description (P)	0.79 (0.23)
Standardised P	0.92 (0.74)

The 57 patients, on average, estimated their present heath state utility as a value of 0.79. In conclusion, despite several changes in the instrument measure, the patient quality of life with an important weight of pain have assessed their current health in a quality of life between the high and low states.

Author: Krahn et al. 2003[76]

Title: Patient and community preferences for outcomes in prostate cancer

141 prostate cancer patients were recruited to evaluate preferences for outcomes for two main health states (non-metastatic and metastatic disease) using rating scale (RS) and standard gamble (SG) methods. The aim was to assess the impact of sexual, urinary and bowel dysfunction on and highlight the differences between valuations based on community and patient preferences.

In order to assess the differences between the separate sources of preferences, patients' utilities were elicited from a disease-specific quality of life measure: PORPUS (Patient Orientated Prostate Utility Scale). Community preferences were assessed based on the patient descriptions provided based on their responses to 2 separate generic quality of life questionnaires: HUI (Health Utilities Index) and QWB (Quality of Well Being Scale).

PORPUS is an instrument composed of 10 psychometric attributes: pain and disturbing body sensations, energy, support from family and friends, communications with doctor, emotional well-being, urinary frequency and urgency, leaking urine and poor bladder control, sexual function, sexual interest and drive, bowel problems. The HUI has 8 attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain. The QWB has 3 attributes: mobility, physical activity, and social activity. The HUI and QWB have two components, a health state classification system and a system of utility weights. Hence, patients were used to classify their current health state in the context of the descriptive system and weights were subsequently applied based on community values.

The mean quality of life scores elicited from community and patients are presented in Table 4. In summary, the mean utilities elicited using SG were higher than RS utilities. The valuations based on the disease-specific measure (PORPUS) were closer to the generic measure assessed using SG (HUI) than that based on a RS approach (QWB). Finally, patients appeared to value their current health state higher than the valuations based on community preferences.

Table 4: Mean quality of life scores

		Standard Gamble utilities		**Rating Scale utilities**	
	N	PORPUS U-SG	HUI	PORPUS U-RS	QWB
All patients	141	0.86	0.80	0.79	0.65
Non metastatic cancer	110	0.86	0.80	0.80	0.66
Metastatic cancer	31	0.85	0.81	0.75	0.62

Author: Sandblom et al. 2004[77]

Title: A population-based study of pain and quality of life during the year before death in men with prostate cancer

1442 patients with prostate cancer received a questionnaire to evaluate the pain and health quality of life with prostate cancer. 1237 patients (635 with palliative treatment, 383 with watchful waiting and 219 with treatment with curative intent) responded to the questionnaire.

The questionnaire was a combination of EuroQol, two parts of the Brief Pain Inventory form (BPI) and eight specially designed questions. The EuroQol is a generic (non disease-specific) instrument, comprising 5 health dimensions (and three levels of severity): mobility, self-care, usual activities, pain and anxiety/depression (derived to EQ-5D). A value score, based on societal valuations, is attached to the different combinations of these dimensions. In addition a visual analogue scale (VAS), providing a rating-scale measurement, is included.

The two parts of BPI included in the questionnaire comprised four questions related to the severity of pain, seven questions assessing the pain interference with daily function. The eight specially designed questions were related to the effectiveness of pain treatment.

A pain management index (PMI) was determined by subtracting the rating of worst pain on the BPI questionnaire from a score corresponding to the strongest prescribed analgesic as reported by the respondent. The strongest prescribed analgesic score was defined as 0 for no analgesic, 1 for non-opioids, 2 for opioids for moderate pain, and 3 for opioids severe pain. Based on the worst pain as stated in the BPI questionnaire, the pain score (0-10) was categorised as 0 for no pain (rating 0), 1 for mild pain (rating 1-3), 2 moderate pain (rating 4-7) and 3 for severe pain (rating 8-10).
A negative score indicates under-treatment of the pain.

Among the 1237 patients who responded to the questionnaire, 66 died of prostate cancer before the end of the year 2000. The patients' characteristics are presented Table 5.

Table 5: Distribution of age, ratings of quality of life and number of patients taking strong opioids for patients who died of prostate cancer, patients who died of other causes and patients still alive

	Died of prostate cancer	Died of other causes	Still alive 31 December 2000
Number	66	100	1076
Age (years, ± s.d.)	76 ± 10	82 ± 6	77 ± 8
Eq5D score (± 95% confidence interval)	0.538 ± 0.077	0.564 ± 0.067	0.770 ± 0.015
EuroQOL VAS (± 95% confidence interval)	54.0 ± 5.2	53.2 ± 4.6	70.0 ± 1.2
Number of patients receiving strong opioids	17 (25.8%)	3 (3.0%)	15(1.4%)

During the last 12 months, the average of quality of life of the 66 patients who died of prostate cancer was a utility value of 0.54. There were only minor non-significant differences in health-related quality of life between those who died of prostate cancer (0.538 ± 0.077) and those who died of other causes (0.564 ± 0.067). The men who died of prostate cancer were found to report significantly worse pain in the last week than men who died of other causes.

A distribution of ratings' quality of life among patients who died of prostate cancer was also categorised for their last 16 months of life, as shown in Table 6.
Four values were presented, corresponding to 4 equal periods of the remaining patient lifetime, 16-12 months, 12-8 months, 8-4 months and 4-0 months.

Table 6: Quality of life

	16-12 months	12-8 months	8-4 months	4-0 months
EuroQol VAS (±	0.57 ± 0.06	0.57 ± 0.06	0.53 ± 0.06	0.45 ± 0.09

95% confidence interval)				
EQ-5D score (± 95% confidence interval)	0.58 ± 0.08	0.58 ± 0.1	0.52 ± 0.08	0.46 ± 0.12

The results presented in Table 6 demonstrate that the patients' prostate cancer quality of life appeared to decrease during the last year of life.

In conclusion, the quality of life in the population of men with prostate cancer decreases during the final year of life, especially during the final 4 months. The quality of life of prostate cancer patients in the last week could be improved with an optimised pain treatment.

Author: Volk et al. 2004[78]

Title: Preferences of husbands and wives for outcomes of prostate cancer screening and treatment

In this study 168 male patients (age mean = 56.4 years) who had a partner or spouse were recruited to investigate the preference for the outcomes of prostate cancer screening and treatment, and quality of life with metastatic prostate cancer. Utility assessments were obtained using 3 phases.

The first phase involved a detailed education period with descriptions of prostate cancer. Metastatic (advanced) prostate cancer was described in two health states corresponding to hormonally responsive prostate cancer and hormonally refractory prostate cancer.

- The hormonally responsive prostate cancer state was a cancer that has spread to other parts of the body. The purpose of the treatment is to slow the growth of prostate cancer cells by stopping the production of testosterone.
- The hormonally refractory prostate cancer state was a cancer that has spread throughout the body. Hormone treatment is no longer effective. The purpose of the treatment is to slow the spread of disease and control symptoms, in particular pain.

The descriptions included treatment complications involving sexual function, urinary and rectal tracts, and a summary of their possible treatment. A utility assessment was undertaken to measure the impact of each complications on the health-related quality of life of metastatic prostate cancer.

In the second phase a scaling technique was involved where the subject ranked each health states on a continuum from 0 (death) to 100 (perfect health).

Finally, in the third phase, the time trade-off method determined the point of indifference between a period of time in an outcome state and a shorter period of time in perfect health.
(NB: The maximum period of time in the health state was based on the husband's life expectancy, as determined by U.S life tables).

The metastatic prostate cancer preferences were measured as utilities. The results for the two metastatic prostate cancer health states, ranging from 0.0 (death) to 1.0 (perfect or full health), are presented in Table 7.

Table 7: Descriptive Statistics for TTO Utilities by Subjects' Perspectives

Prostate Cancer	Hormonally responsive prostate cancer				Hormonally refractory prostate cancer (HRPC)			
Data	Mean	Median	25th percentile	75th percentile	Mean	Median	25th percentile	75th percentile
Husbands	0.72	0.79	0.55	0.96	0.55	0.50	0.33	0.78
Wives	0.86	0.94	0.82	1.00	0.66	0.68	0.43	0.92
Couples	0.83	0.90	0.73	1.00	0.62	0.65	0.41	0.89

For each health state husbands reported lower utilities than did their wives. The largest absolute differences in median utilities between husbands and wives were observed for hormonally refractory prostate cancer. There was a low correlation between husbands and wives' time trade-off utilities.

This study demonstrates that male primary care patients who are candidates for prostate cancer screening have preferences for the outcomes of prostate cancer treatment and quality of life with advanced prostate cancer that differ from the

preferences of their wives. In conclusion, most husbands would be willing to trade some longevity to avoid the health metastatic prostate cancer scenarios.

Author: Stewart et al. 2005[79]

Title: Utilities for prostate cancer health states in men aged 60 and older

162 men aged 60 and older (including 52% with prostate cancer) were recruited to provide valuations for 19 health states associated with prostate cancer or its treatment using approaches based on standard gamble. Similar ratings were also obtained using TTO and Visual Analogue Scale (VAS) approaches, although the data for these was not reported in the paper.

The 162 subjects randomly rated 9 of the 19 health states. These 19 health states were then combined and used to assess four main health states. These health states comprised three "asymptomatic" states with a different probability of tumour spread, plus a terminal "symptomatic" health state.

In order to measure SG utilities, respondents were asked to imagine that they were in one of the four health states presented, and that there was a treatment that could cure them but with an associated risk of mortality. A ping-pong method was then used to help the respondent to choose the maximum risk of death he would accept as a consequence of treatment. The utility for the health state was then estimated using the inverse of the accepted level of risk, transformed to a 0-1 scale.

Most respondents were reported to have logically ordered ratings, and the mean SG utilities are shown in Table 8.

Table 8: Mean Standard Gamble Utilities for health states

Health State	Mean	Standard deviation	Median	Range	N
Cancer with 20% chance of spread	0.84	0.19	0.89	0.09-1.0	88
Cancer with 40%	0.81	0.18	0.81	0.01-1.0	49

chance of spread					
Cancer with 75% chance of spread	0.71	0.24	0.79	0.01-1.0	53
Spread asymptomatic	0.67	0.24	0.70	0.01-1.0	46
Metastatic cancer	0.25	0.11	0.11	0-0.9	54

The mean SG utilities for the different health states revealed a lower quality of life associated with an increasing probability of tumour spread (0.84 to 0.67). The utility value estimated for the terminal health state was considerably lower than the asymptomatic states (0.25).

Although data based on other approaches (TTO and VAS) were not reported, the mean valuations provided for most health states were described as being similar using TTO and SG and significantly lower using the Visual Analog Scale (VAS).

Appendix 10.11. Drug cost calculations for each comparator

Table 1: Drug and Administration costs for D+P (3-weekly)

D+P (3-weekly)	
Dose	
mean body surface (m^2)	1.9
dose per cycle (mg/m^2)	75
total dose per cycle (mg)	142.5
no of cycles	7.3
Total cumulated dose	1040.25
Drug cost	
Docetaxel	£7,807.35
Prednisone	£7.45
Dexamethasone	£43.36
Total drug cost	£7,858.16
Administration costs	£1,295.46
Total drug and admin cost	£ 9,153.62

Table 2: Drug and Administration costs for M+P

M+P	
Dose	
mean body surface (m^2)	1.9
dose per cycle (mg/m^2)	12
total dose per cycle (mg)	22.8
no of cycles	5.9
Total cumulated dose	134.52
Drug cost	
Mitoxantrone	£998.58
Prednisone	£6.02
Total drug cost	£1,004.59
Administration costs	£1,047.01
Total drug and admin cost	£ 2,051.60

Table 3: Drug and Administration costs for P

P	
Drug cost	
Prednisone	£1.48
Total drug cost per cycle	£1.48

Table 4: Drug and Administration costs for D+P (weekly)

D+P (weekly)	
Dose	
mean body surface (m^2)	1.9
dose per cycle (mg/m^2)	150
total dose per cycle (mg)	285
no of cycles	3.7
Total cumulated dose	1054.5
Drug cost	
Docetaxel	£18,925.50
Prednisone	£7.55
Dexamethasone	£36.63
Total drug cost	£18,969.68
Administration costs	£656.60
Total drug and admin cost	£19,626.28

Table 5: Drug and Administration costs for D+E

D+E	
Dose	
mean body surface (m^2)	1.9
dose per cycle (mg/m^2)	60
total dose per cycle (mg)	114
no of cycles	7.3
Total cumulated dose	832.2
Drug cost	
Docetaxel	£6,279.83
Estramustine	£375.10
Warfarin	£15.22
Dexamethasone	£364.85
Total drug cost	£7,035.00
Administration costs	£1,295.46
Total drug and admin cost	£ 8,330.46

Table 6: Drug and Administration costs for D+E+P (70)

D+E+P (70)	
Dose	
mean body surface (m^2)	1.9
dose per cycle (mg/m^2)	70
total dose per cycle (mg)	133
no of cycles	7.3
Total cumulated dose	970.9
Drug cost	
Docetaxel	£7467.90
Prednisone	£7.45
Estramustine	£675.19
Warfarin	£15.22
Dexamethasone	£364.85

Total drug cost	£8,530.61
Administration costs	£1,295.46
Total drug and admin cost	£ 9,826.07

Table 7: Drug and Administration costs for D+E+P (35)

D+E+P (35)	
Dose	
mean body surface (m^2)	1.9
dose per cycle (mg/m^2)	35
total dose per cycle (mg)	66.5
no of cycles	7.3
Total cumulated dose	485.45
Drug cost	
Docetaxel	£7,807.35
Prednisone	£7.45
Estramustine	£675.19
Warfarin	£15.22
Dexamethasone	£729.71
Total drug cost	£9,234.91
Administration costs	£2,590.92
Total drug and admin cost	£11,825.83

Table 8: Drug and Administration costs for M+P+C

M+P+C	
Dose	
mean body surface (m^2)	1.9
dose per cycle (mg/m^2)	12
total dose per cycle (mg)	22.8
no of cycles	5.9
Total cumulated dose	134.52
Drug cost	
Mitoxantrone	£998.58
Prednisone	£6.02
Clodronate	£325.09
Total drug cost	£1,329.68
Administration costs	£1,047.01
Total drug and admin cost	£ 2,376.99

Appendix 10.12: WinBUGS code for adverse events analysis

```
model{

for (j in 1:6) { delta[j]~ dnorm (0.0,0.0001)}
m.r~dnorm(0.0,0.001)
t.r~dgamma(3,1)

for (j in 1:4){ mu.r[j]~dnorm(m.r,t.r) }

for (i in 1:10){ logit(p[i])<-mu.r[study[i]] + equals(treat[i],2) * delta[1] +
equals(treat[i],3) * delta[2] + equals(treat[i],4) * delta[3] + equals(treat[i],5) * delta[4]
+ equals(treat[i],6) * delta[5] + equals(treat[i],7) * delta[6]}

for (i in 1:10){ r[i]~dbin(p[i],n[i]) }
logit(t[1])<-m.r
for (j in 2: 7) {logit(t[j]) <- m.r + delta[j-1] }
}

list( r=c(154,144,118,25,4,27,176,109,22,15),
n=c(335,334,335,44,44,42,330,328,80,81),
study=c(1,1,1,2,2,2,3,3,4,4),
treat=c(2,3,4,5,6,4,7,4,4,1))

list(m.r=0, t.r=1)
```

node	mean	sd	MC error	2.5%	median	97.5%	start	sample	
	t[1]	0.2735	0.09251	0.005113	0.1227	0.2632	0.4863	10001	10000
	t[2]	0.4955	0.08886	0.001438	0.3224	0.4951	0.6763	10001	10000
	t[3]	0.4676	0.08811	0.001416	0.2987	0.4648	0.6516	10001	10000
	t[4]	0.3897	0.07964	0.001036	0.2431	0.3862	0.5622	10001	10000
	t[5]	0.3745	0.112	0.001731	0.1758	0.368	0.6069	10001	10000
	t[6]	0.04532	0.02947	3.936E-4	0.00921	0.03852	0.122	10001	10000
	t[7]	0.5872	0.08663	0.00132	0.4094	0.5889	0.7532	10001	10000

#t[1] = P
#t[2] = D+P (3-weekly)
#t[3] = D+P (weekly)
#t[4] = M+P
#t[5] = D+E+P (70)
#t[6] = D+E+P (35)
#t[7] = D+E

Appendix 10.13 Health state descriptions for adverse event analysis

SCENARIO: MODERATE DISEASE (CHAPMAN B)

- You have a bearable amount of pain and it is moderately well controlled by medication
- You feel tense, worried, irritable, sad, or depressed sometimes (only once or twice a week)
- Your ability to have sex and to enjoy it as been affected a fair amount by your condition
- You have occasional difficulties or problems with urinating or bowel function (only once or twice a week)
- You have some difficulty doing usual activities.
- You do less than before and are tired quite a bit of the time.
- You need some assistance with some daily activities (for example, dressing, washing, using the toilet)

SCENARIO: MODERATE DISEASE (CHAPMAN B) + TAXANES AEs

- You have a bearable amount of pain and it is moderately well controlled by medication
- You feel tense, worried, irritable, sad, or depressed sometimes (only once or twice a week)
- Your ability to have sex and to enjoy it as been affected a fair amount by your condition
- You have occasional difficulties or problems with urinating or bowel function (only once or twice a week)
- You have some difficulty doing usual activities.
- You do less than before and are tired quite a bit of the time.
- You need some assistance with some daily activities (for example, dressing, washing, using the toilet)

In this scenario you are taking treatment for your condition, which may have the following *additional* effects:

- You are at risk of serious infections and may spend time in hospital receiving treatment for these
- You feel weak and tired much of the time
- Your hair has fallen out

- You have moderate diarrhoea and feel nauseated
- Your appetite is poor
- You may feel a little short of breath on exertion
- Your ankles may become swollen and this may affect your ability to walk
- You experience tingling and numbness in your hands and feet which is sometimes quite severe

SCENARIO: MODERATE DISEASE (CHAPMAN B) + MITOXANTRONE AEs

- You have a bearable amount of pain and it is moderately well controlled by medication
- You feel tense, worried, irritable, sad, or depressed sometimes (only once or twice a week)
- Your ability to have sex and to enjoy it as been affected a fair amount by your condition
- You have occasional difficulties or problems with urinating or bowel function (only once or twice a week)
- You have some difficulty doing usual activities.
- You do less than before and are tired quite a bit of the time.
- You need some assistance with some daily activities (for example, dressing, washing, using the toilet)

In this scenario you are taking treatment for your condition, which may have the following *additional* effects:

- You feel weak and tired much of the time
- You bruise more easily than usual
- You feel short of breath, particularly when lying flat, and have swollen ankles which may affect your ability to walk
- You experience pains in your joints

SCENARIO: MODERATE DISEASE (CHAPMAN B) + ESTRAMUSTINE AEs

- You have a bearable amount of pain and it is moderately well controlled by medication
- You feel tense, worried, irritable, sad, or depressed sometimes (only once or twice a week)

- Your ability to have sex and to enjoy it as been affected a fair amount by your condition
- You have occasional difficulties or problems with urinating or bowel function (only once or twice a week)
- You have some difficulty doing usual activities.
- You do less than before and are tired quite a bit of the time.
- You need some assistance with some daily activities (for example, dressing, washing, using the toilet)

In this scenario you are taking treatment for your condition, which may have the following *additional* effects:

- Severe vomiting
- Breast development (in men)
- Chest pain

Appendix 10.14 Health state descriptions based on FACT-P

SCENARIO 1: ADVANCED DISEASE – EARLY (FACT-P)

This scenario is based on a questionnaire which uses the following phrases to describe the level of impact of symptoms and impairments:

- Not at all
- A little bit
- Somewhat
- Quite a bit
- Very much

- You have a little nausea and some lack of energy
- You worry quite a bit about your condition getting worse and about dying.
- You feel somewhat sad and nervous
- Your ability to work, your enjoyment of life and the quality of your sleep are somewhat reduced
- Your appetite is restricted a little bit and you have lost a moderate amount of weight
- You have general aches and pains that bother you somewhat
- You experience significant pain in certain parts of your body which sometimes keeps you from doing things you want to do
- You have a little trouble moving your bowels
- You find it somewhat difficult to urinate and you may urinate more frequently than usual. These problems limit your activities somewhat.
- Your ability to have sex is severely affected by your condition

SCENARIO 2: ADVANCED DISEASE – MODERATE (FACT-P)

This scenario is based on a questionnaire which uses the following phrases to describe the level of impact of symptoms and impairments:

- Not at all
- A little bit
- Somewhat
- Quite a bit
- Very much

- You feel somewhat nauseated and feel lack of energy quite a bit
- You worry quite a bit about your condition getting worse and about dying
- You feel sad and nervous quite a bit
- Your ability to work, your enjoyment of life and the quality of your sleep are reduced quite a bit
- Your appetite is somewhat reduced and you have lost a quite a bit of weight
- You have general aches and pains that bother you quite a bit
- You often experience moderate to severe pain in certain parts of your body, particularly in your bones, which often keeps you from doing things you want to do
- You have a some trouble moving your bowels
- You find it somewhat difficult to urinate and you may urinate more frequently than usual. These problems limit your activities somewhat.
- Your ability to have sex is severely affected by your condition

SCENARIO 3: ADVANCED DISEASE – LATE (FACT-P)

This scenario is based on a questionnaire which uses the following phrases to describe the level of impact of symptoms and impairments:

- ❑ Not at all
- ❑ A little bit
- ❑ Somewhat
- ❑ Quite a bit
- ❑ Very much

- You feel nausea quite a bit and are extremely tired a lot of the time
- You worry very much about your condition getting worse and sometimes feel hopeless about the future
- You feel very sad and nervous
- Your ability to work, your enjoyment of life and the quality of your sleep are very much reduced
- Your appetite is reduced quite a bit and you have lost a lot of weight
- You have general aches and pains that bother you very much
- You often experience severe pain in certain parts of your body, particularly in your bones, which often keeps you from doing things you want to do

- You occasionally have a some trouble moving your bowels
- You find it somewhat difficult to urinate and you may urinate more frequently than usual. These problems limit your activities somewhat.
- Your ability to have sex is severely affected by your condition