National Institute for Health and Care Excellence

Guideline version (Draft)

Prostate cancer: diagnosis and management

[B] Evidence review for docetaxel in people with hormone sensitive prostate cancer

NICE guideline <number>

Evidence review

April 2019

Draft for Consultation

These evidence reviews were developed by the NICE Guideline Updates Team

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Docetaxel and hormone-sensitive locally advanced and metastatic prostate cancer

Review questions

- What is the most clinically- and cost-effective scheduling of docetaxel added to standard treatment for the treatment of hormone-sensitive locally-advanced prostate cancer?
- What is the most clinically- and cost-effective scheduling of docetaxel added to standard treatment for the treatment of hormone-sensitive metastatic prostate cancer?

Introduction

The aim of the review was to determine the effectiveness of the use of docetaxel in people with hormone-sensitive metastatic and people with hormone-sensitive locally-advanced prostate cancer. The committee decided to refer to locally advanced prostate cancer as high risk prostate cancer due to a lack of universal definition. Therefore from this point onwards the term “high risk” prostate cancer is used. Please see full protocols in Appendix A.

Table 1: PICO table

Population	• People with hormone-sensitive metastatic prostate cancer • People with hormone-sensitive high risk prostate cancer
Interventions	Docetaxel added to standard treatment (as defined by the trials)
Comparator	• Placebo added to standard treatment • Standard treatment alone

Outcomes	• Overall survival
	• Progression free survival (as defined by the trials)
	• Prostate cancer-specific mortality
	• Metastases-free survival
	• Treatment-related mortality
	• Health related quality of life – (for example EORTC, EPIC instruments)
	• Number of severe adverse events
	  • Sepsis
	  • Pancytopenia
	  • Number of treatment discontinuations due to adverse events

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A, and the methods section in appendix B.

Declarations of interest were recorded according to NICE’s 2014 and 2018 conflicts of interest policies.

Clinical evidence

Included studies

This review was conducted as part of a larger update of the NICE Prostate Cancer guideline (CG175).

A systematic literature search for randomised controlled trials (RCTs) and systematic reviews with no date limit yielded 4,024 references. These were screened on title and abstract, with 138 full-text papers ordered as potentially relevant systematic reviews or RCTs. RCTs were excluded if they did not meet the criteria of enrolling patients with hormone-sensitive metastatic or locally advanced prostate cancer in a docetaxel randomised controlled trial. Studies were further excluded at data extraction if they did not match any of the outcomes specified in the protocol.

Seven papers were included after full text screening: there were 6 RCTs and 1 systematic review. 7 systematic reviews were identified, however; 6 were excluded because the randomised control studies included in these systematic reviews were already identified at full text screening and 1 systematic review was included as an association study to supplement data that was not included in the original article (see evidence tables for details – appendix E).

Multiple papers reporting results of the same study were identified and collated, so that each study rather than individual reports was the unit of interest in the review.

Please note one study was included for both locally-advanced and metastatic prostate cancer, therefore overall a total of 6 unique studies were included in this review.

A second set of searches was conducted at the end of the guideline development process for all updated review questions using the original search strategies to capture papers published whilst the guideline was being developed. These searches, which included articles up to August 2018, returned 398 references for this review question. These were screened on title and abstract and no additional relevant references were found.

For the full evidence tables and full GRADE profiles for included studies, please see appendix E and appendix G.

Excluded studies

Details of the studies excluded at full-text review are given in appendix H along with a reason for their exclusion.

Summary of clinical studies included in the evidence review

Hormone-sensitive locally-advanced prostate cancer

Three randomised controlled trials were included in this review for hormone-sensitive high risk prostate cancer. All three unique studies were directly applicable as they matched the protocol.

Table 2: Docetaxel doses used in the studies

Study	Study arms	Doses
STAMPEDE James 2016 (United Kingdom)	ADT (plus radiotherapy) versus ADT plus docetaxel	75mg/m2 every 3 weeks for 6 cycles with 10mg of prednisone daily and standard premedication before each injection

STAMPEDE James 2016 (United Kingdom) **High-risk locally advanced PC**	ADT plus zoledronic acid versus ADT plus zoledronic acid plus docetaxel	75mg/m2 of docetaxel every 3 weeks for 6 cycles with 10mg of prednisone daily and standard premedication before each injection 4mg of zoledronic acid every 3-4 weeks for 2 years
GETUG-12 Fizazi 2015 (France) **High-risk localised PC**	ADT versus ADT plus docetaxel plus estramustine	70mg/m2 of docetaxel every 3 weeks for 4 cycles preceded by 50mg prednisone the day before, 3 doses of 50mg on the day of infusion and two doses of 50mg the day after Estramustine orally for 5 days consecutively, once every 3 weeks starting on day 1 at a dose of 10mg/kg/day. Daily dose of aspirin 300mg. ADT (Goserelin) 10.8mg every 3 months for 3 years
TAX 3501 Schweizer 2014 108 countries including 45 centres in Europe **High-risk PC**	ADT versus ADT plus docetaxel	75mg/m2 of docetaxel every 3 weeks for 6 cycles (there was no mentioning of steroids use during or after treatment) ADT (leuprolide) 22.5mg every 3 months for 18 months

Outcomes and sample sizes

The reported outcomes where data was extractable were

- Overall survival
- Clinical progression-free survival was described differently in each study-:
  Failure-free survival was defined as time from randomisation to first evidence of at least one of: biochemical failure (defined as a rise of 50% above the within-24-week nadir and above 4ng/ml confirmed by rest or treatment), progression either locally, in lymph nodes, or in distant metastases or death from cancer (STAMPEDE James et al. 2016)
  Progression-free survival was defined as PSA progression (the first PSA increase to ≥0.4ng/ml, with a confirmatory PSA obtained within 2 weeks of the initially elevated value) , radiographic, or histological disease progression after systemic treatment or death from any cause, whichever came first as measured from the time of surgery. Progression free survival was measured from the date of disease progression (TAX 3501 Schweizer et al. 2013)
  Relapse-free survival was defined as biochemical failure (an increase in serum PSA of more than 0.2ng/ml above the nadir, confirmed by another sample), onset of metastases on imaging, proven local relapse, use of salvage treatment and death.
- Prostate cancer-specific survival (GETUG-12 Fizazi et al. 2015)
- All-cause mortality

The sample sizes ranged from 228 to 1,776 participants across the studies

Hormone-sensitive metastatic prostate cancer

Three randomised controlled trials where included in this review. All three unique studies where directly applicable as they adhered to the protocol.

Table 3: Docetaxel doses used in the studies

Study (location)	Study arms (total sample size)	Doses
STAMPEDE James 2016 (United Kingdom)	ADT (plus radiotherapy) versus ADT plus docetaxel	75mg/m2 every 3 weeks for 6 cycles with 10mg of prednisolone daily and standard premedication before each injection
STAMPEDE James 2016 (United Kingdom)	ADT plus zoledronic acid versus ADT plus zoledronic acid plus docetaxel	75mg/m2 of docetaxel every 3 weeks for 6 cycles with 10mg of prednisolone daily and standard premedication before each injection 4mg of zoledronic acid every 3-4 weeks for 2 years
GETUG-15 Gravis 2013 (France)	ADT alone versus ADT plus docetaxel	75mg/m^2 of intravenous docetaxel in a 250cm^3 5% glucose solution in the course of 1h on the first of each 21 day cycle for up to 9 cycles. Premedication with corticosteroid (8mg dexamethasone or equivalent) given orally in the evening before the infusion of docetaxel on the day of docetaxel infusion and on the next day.
CHAARTED Sweeney 2015 (USA)	ADT (luteinizing hormone-releasing hormone agonist or luteinizing hormone-releasing hormone antagonist or surgical castration) versus ADT plus docetaxel	75mg/m2 of docetaxel every 3 weeks for 6 cycles, with 8mg of oral dexamethasone at 12 hours, 3 hours and 1 hour before docetaxel infusion. Daily prednisolone was not required.

Outcomes and sample sizes

The reported outcomes where data was extractable were

- Overall survival
- Clinical progression-free survival defined as failure-free survival expressed as time from randomisation to first evidence of at least one of-: biochemical failure (defined as a rise of 50% above the within-24-week nadir and above 4ng/ml confirmed by rest or treatment), progression either locally, in lymph nodes, or in distant metastases or death from cancer (STAMPEDE James et al. 2016)
- Biochemical progression free survival.
- Prostate cancer-specific survival
- Quality of life

The sample sizes ranged from 385 to 1,776 participants across the studies

Adverse outcomes were only reported for the treatment arm, therefore analysis could not be carried out. An adverse outcome table is included in appendix E.

Quality assessment of clinical studies included in the evidence review

See appendix G for full GRADE tables.

See full evidence tables in appendix E.

Economic evidence

Standard health economic filters were applied to the clinical search strategy for this question. Details are provided in appendix C. In total, 1,049 records were returned, of which 1,041 could be confidently excluded on sifting of titles and abstracts. The remaining 8 studies were ordered to be reviewed. Out of 8 reviewed in full text, 7 were found not to be relevant. This left one unique cost–utility analysis (CUA) that was selectively excluded, as it adopted a Chinese perspective.

Included studies

One study was identified by the committee (Woods et al. 2018). The formal publication of this analysis postdates the searches for this guideline; however, the authors made a

prepublication draft available to the committee. This had no material differences from the version that was subsequently published.

Excluded studies

For a list of excluded studies see appendix H

Summary of studies included in the economic evidence review

Wood et al. (2018) developed an economic model for lifetime health outcomes and costs, using data captured in STAMPEDE RCT (James et al., 2016) and adopting the perspective of the UK NHS and personal and social services.

Patients at trial entry could have either non-metastatic disease (defined as no metastases or those confined to nonregional lymph nodes only – M0/M1a lymph node), or metastatic disease (defined as bone or visceral metastases – M1 bone/visceral). A patient-level state-transition model was constructed, using the characteristics of the cohort enrolled at STAMPEDE to produce lifetime predictions. Simulated patients entered the model in the non-progressed (hormone-naïve) state. Then, they may experience progression to castrate-resistant prostate cancer (CRPC), while also developing new or more severe metastases. It was assumed that data from the metastatic population at baseline can be applied to patients who were non-metastatic at baseline but developed metastasis later on. Severity in CRPC is categorised from least to most severe (i.e. M0 or M1 lymph node, M1 bone, M1 bone+skeletal-related event, M1 visceral). Patients could move to death from any health state; the model distinguished between prostate cancer death and other causes death. A parametric multi-state survival modelling approach, analysing time to first/subsequent events, was applied to estimate the transition probability between the health states within the model. This approach does not require the proportional hazard assumption and is adequately flexible to capture the rate at which the event of progression occurs, even if it varies with time.

Health-related utilities used in the model were derived from the STAMPEDE data using the EQ-5D questionnaire completed by patients. Additional disutility was applied when patients received docetaxel and that was assumed to last for a year.

The authors found that docetaxel administered to metastatic patients along with standard care appeared to be cost effective, with an ICER of £5,514 per QALY gained compared with standard care only. For non-metastatic patients, docetaxel was shown to be dominant, producing more QALYs (0.39) and saving costs (-£251) compared with standard care only. Probabilistic sensitivity analysis results showed that at a cost-effectiveness threshold of £20,000 per QALY, docetaxel was cost-effective in >99% of the iterations using the base-case model inputs in both non-metastatic and metastatic populations. Using the British National Formulary price for docetaxel, which is considerably higher than what the NHS pays, in a sensitivity analysis resulted in the ICER being at £10,610 and £13,868 per QALY in non-metastatic and metastatic populations respectively.

Economic model

This question was not prioritised for economic modelling.

Evidence statements

Hormone-sensitive high risk prostate cancer

Moderate-quality evidence from 1 RCT reporting data on 1,190 people with hormone-sensitive locally-advanced prostate cancer could not differentiate overall survival in those

receiving docetaxel (combined with either zoledronic acid and standard care or standard care alone) compared to those receiving standard care alone.

Moderate-quality to high-quality evidence from up to 3 RCTs reporting data on up to 1,791 people with hormone-sensitive high risk prostate cancer found clinical progression-free survival was prolonged in those receiving docetaxel compared to standard care alone, at doses of either 75mg/m^2 administered every 3 weeks for 6 cycles or 70mg/m^2 administered every 3 weeks for 4 cycles. This improvement was observed in those with high risk disease criterion of either Gleason score less than 8 or clinical stage T3-T4.

Very-low to moderate-quality evidence from up to 2 RCTs reporting data on up to 1,791 people with hormone-sensitive high risk prostate cancer found there was no meaningful difference in the number of people who developed metastases, all-cause mortality and prostate cancer-specific mortality in those receiving docetaxel (combined with either estramustine and androgen deprivation therapy (ADT), zoledronic acid and standard care or standard care alone) compared to standard care alone (defined as either ADT or hormonal therapy or radiotherapy).

One directly applicable cost–utility analysis with potentially serious limitations found that, compared with standard care alone, the addition of 6 3-weekly cycles of docetaxel results in increased quality-adjusted life expectancy and cost savings in people with newly diagnosed locally advanced prostate cancer. The probability that docetaxel is associated with an ICER better than £20,000/QALY was greater than 99%.

Hormone-sensitive metastatic prostate cancer

High-quality evidence from up to 2 RCTs reporting data on up to 1,442 people with hormone-sensitive metastatic prostate cancer found that quality of life scores during the treatment phase worsened in those receiving docetaxel compared to those receiving standard care alone (defined as either hormone therapy or androgen deprivation therapy).

Moderate-quality to high-quality evidence from up to 3 RCTs reporting data on up to 2,617 people with hormone-sensitive metastatic prostate cancer found overall survival, prostate cancer-specific survival, clinical progression-free survival and biochemical progression-free survival was prolonged in those receiving docetaxel compared to those receiving standard care alone (defined as androgen deprivation therapy). Subgroup analysis of the evidence showed there was improved overall survival in those receiving a dose of 75mg/m^2 of docetaxel delivered every 3 weeks for up to 6 cycles and those with high volume disease and could not differentiate overall survival in those receiving the same dose of docetaxel delivered every 3 weeks for up to 9 cycles and those with low volume disease.

One directly applicable cost–utility analysis with minor limitations found that, compared with standard care alone, the addition of 6 3-weekly cycles of docetaxel results in increased quality-adjusted life expectancy and increased costs in people with newly diagnosed metastatic prostate cancer, resulting in an ICER of £5,500/QALY gained. The probability that docetaxel is associated with an ICER better than £20,000/QALY was greater than 99%.

Recommendations

B1. Offer docetaxel chemotherapy to people with newly diagnosed metastatic prostate cancer who do not have significant comorbidities:

- start treatment within 12 weeks of starting androgen deprivation therapy, and
- use six 3-weekly cycles at a dose of 75 mg/m^2 (with or without daily prednisolone). **[2019]**

B2. Discuss the option of docetaxel chemotherapy with people who have newly diagnosed non-metastatic prostate cancer[a] who:

- are starting long-term androgen deprivation therapy **and**
- have no significant comorbidities **and**
- have high-risk disease, as shown by:
  - T3/T4 staging or
  - Gleason score 8–10 or
  - PSA greater than 40 ng/ml.

Explain the benefits and harms (see **Error! Reference source not found.**4) and make a shared decision about whether the person should have this treatment. **[2019]**

B3. For people having docetaxel chemotherapy:

- start treatment within 12 weeks of starting androgen deprivation therapy
- use six 3-weekly cycles at a dose of 75 mg/m^2 (with or without daily prednisolone). **[2019]**

Table 4: Factors to consider when discussing the option of docetaxel chemotherapy for people with high-risk, non-metastatic in prostate cancer

What does treatment with docetaxel involve?	Docetaxel chemotherapy is given at 6 appointments, each 3 weeks apart. It is given as an intravenous infusion that takes about 1 hour.
What are the benefits of docetaxel treatment for people with high-risk, non-metastatic prostate cancer?	• There is clear, high-quality evidence that docetaxel chemotherapy delays disease progression in people with high-risk, non-metastatic disease. • In a large UK randomised trial, the average person who did not receive docetaxel experienced disease progression about 5 years after the start of the trial, whereas the average person receiving docetaxel experienced disease progression after about 6 years. • We do not yet know whether docetaxel improves survival in people with high-risk, non-metastatic disease and we will only be confident about whether it does when trials have been running for longer. • In a large UK randomised trial, 80 out of 100 people with high-risk disease who did not receive docetaxel were still alive after 5 years compared to 84 out of 100 people who did. However, this difference could be because of chance.
What are the risks associated with docetaxel treatment?	A large UK randomised trial found that: • 15 out of 100 people who took docetaxel developed febrile neutropenia (that is, they got a fever because the chemotherapy had reduced their white blood cells' ability to fight infection). • 1 out of 100 people who took docetaxel died because of infections that, in the opinion of the investigators, they

[a] At the time of consultation (December 2018), docetaxel only has UK marketing authorisation for hormone refractory metastatic prostate cancer. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information

	might not have developed if they had not received docetaxel. • 8 out of 100 people who took docetaxel felt unusually weak or tired. • 8 out of 100 people who took docetaxel experienced gastrointestinal symptoms (including diarrhoea, abdominal pain, constipation and/or vomiting). • 5 out of 100 people who took docetaxel experienced respiratory symptoms (including breathlessness and/or chest infections). • 4 out of 100 people who took docetaxel experienced problems with their nervous systems (for example, numbness or weakness). • 1 out of 100 people who took docetaxel experienced problems with their nails that were serious enough to interfere with their daily lives.

1

Research recommendations

3 What is the prognostic value of different risk stratification methods for people with locally
4 advanced prostate cancer?

Rationale and impact

Why the committee made the recommendations

7 There was good evidence that showed docetaxel improves overall survival, prostate cancer-
8 specific survival and clinical progression-free survival in people with newly diagnosed
9 metastatic prostate cancer who are starting long-term hormone therapy. The committee
10 agreed these benefits outweighed the potential harms of the treatment.

11 The evidence also showed docetaxel slows clinical progression in people with newly
12 diagnosed high-risk non-metastatic cancer starting long-term hormone therapy. However, the
13 evidence did not show any extension of overall survival. Because of the known toxicities
14 associated with docetaxel treatment, the benefits and harms are more finely balanced in this
15 population. As a result, the committee identified this decision as being preference sensitive,
16 and the person's values and preferences are likely to be particularly important in their
17 decision about the best course of action for them.

18 The committee also made a research recommendation as it identified a gap in the evidence.
19 The committee explained that currently there is no universal definition of locally advanced
20 prostate cancer. A risk stratification study will help identify patients at various levels of risks
21 and help tailor treatment according to need.

Impact of the recommendations on practice

23 Off-label use of docetaxel in people diagnosed with hormone-sensitive metastatic prostate
24 cancer is current practice, therefore the recommendation for the metastatic prostate cancer
25 population is likely to have no impact. However, this does not include high-risk non-
26 metastatic prostate cancer. Therefore, the recommendation for this population could result in
27 an increase in the number of people with high-risk non-metastatic prostate cancer receiving
28 docetaxel chemotherapy. Although this could result in an increase in some shorter term costs

to the NHS, the economic evidence showed a reduction in longer-term management costs, with the net effect that docetaxel is likely to be cost-saving in the long term in this population and, once its benefits are also taken into account, almost certain to represent a good use of NHS resources.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that the critical outcomes were overall survival, clinical progression-free survival and adverse events as these had the most impact on the patients. The committee noted that the definition of clinical progression-free survival differed across the studies; however all the studies included biochemical progression (as measured by an increase in prostate-specific antigen [PSA]). The committee raised concerns that this was a laboratory marker, but agreed this was a sufficient marker as an increase in PSA has an impact on the treatment of the patient in practice.

The quality of the evidence

All 6 included studies were at moderate or high risk of bias owing to the lack of blinding of participants and investigators as the studies were open label. The largest study was from the United Kingdom (STAMPEDE (James et al. 2016)). The committee agreed that the evidence presented was representative of current practice and acknowledged that the evidence (especially for high-risk non-metastatic prostate cancer) was likely to become more definitive as more study data becomes available.

The committee was interested in reviewing the evidence for populations with high-risk non-metastatic prostate cancer and those with metastatic prostate cancer. The review question specified high-risk prostate cancer as locally advanced; the committee felt that there was no universal definition of locally advanced or localised prostate cancer. As a result they referred to non-metastatic cancer as just high-risk prostate cancer. The committee agreed to apply the inclusion criteria from studies in non-metastatic disease as the working definition of high-risk prostate cancer for this evidence review.

Three studies (STAMPEDE (James et al. 2016), GETUG-15 (Gravis et al. 2013) and CHAARTED (Sweeney et al.2015)) contributed evidence for the metastatic prostate cancer population group and 3 studies contributed evidence for the high-risk prostate cancer population group (STAMPEDE (James et al. 2016), TAX 3501 (Schweizer et al. 2014) and Getug-12 (Fizazi et al. 2015). The STAMPEDE trial contributed evidence to both populations.

Despite the relatively small number of studies, the committee appreciated that the studies had large sample sizes ranging from 228 to 1,776 participants.

The GETUG-15 study included the estramustine in the same arm as docetaxel. The committee agreed to not downgrade or exclude this study because it that docetaxel given with estramustine was equivalent to docetaxel given with prednisolone in the other studies. This is reflected by the fact that the results from GETUG study was consistent with the results from the other studies in the meta-analysis.

The committee was also interested in the dose and frequency of docetaxel and whether or not daily prednisolone was used in conjunction with docetaxel. Two of the 3 studies (GETUG-12 (Fizazi et al. 2015) and STAMPEDE (James et al, 2016)) whose population had high-risk prostate cancer included prednisolone as part of their treatment. Only one (STAMPEDE (James et al. 2016)) of the metastatic prostate cancer studies included it.

The doses of docetaxel were similar at 75 mg/m^2 in all 3 metastatic prostate cancer studies. However the GETUG-AFU15 (Gravis et al. 2013) study delivered docetaxel for up to 9 cycles every week unlike the STAMPEDE (James et al. 2016) and CHAARTED (Sweeney et al. 2016) studies which delivered for up to 6 cycles.

The committee acknowledged that, though the studies termed clinical progression-free survival as either failure-free survival (STAMPEDE (James et al. 2016)), relapse-free survival (GETUG-12 (Fizazi 2015)), progression-free survival (TAX 3501 (Schweizer et al. 2013)) and clinical progression (CHAARTED (Sweeney et al. 2016) and GETUG-AFU15 (Gravis et al. 2013)), they all included change in prostate-specific antigen in their definitions, among other elements such as death from cancer, distant metastases and proven local relapse.

Overall, when the evidence was assessed using GRADE, the majority of the of it was of moderate to high quality, this was due to precise 95% confidence intervals mean that the studies were not downgraded for imprecision and the objective nature of the outcomes meant that potential sources of bias such as the open-label status of the studies were unlikely to have an impact on the results.

Benefits and harms

Based on the evidence, the benefit of docetaxel for hormone-sensitive metastatic cancer outweighs the harms. The evidence shows that docetaxel can prolong overall survival and clinical progression-free survival in people with newly diagnosed metastatic prostate cancer who are starting long-term hormone therapy (GETUG AFU15 (Gravis et al. 2013), CHAARTED (Sweeney et al. 2016) and STAMPEDE (James et al.2016)). All 3 studies included androgen deprivation therapy and participants were either hormone naïve or hormone sensitive. The committee interpreted this to mean participants were newly diagnosed with metastatic prostate cancer.

The STAMPEDE (James et al. 2016) trial reported that docetaxel chemotherapy is associated with a number of adverse events including infections, febrile neutropenia, gastrointestinal and respiratory symptoms in people with either metastatic or high risk prostate cancer. Because the evidence showed survival benefit in those with hormone-sensitive metastatic cancer, the committee agreed that the benefits of docetaxel chemotherapy outweighed the harm. As a result the committee made a strong recommendation for clinicians to offer docetaxel to those people with hormone-sensitive metastatic prostate cancer.

In addition, the committee was able to specify dose and frequency of treatment because the evidence showed an improvement in survival in studies which considered 75mg/m^2 of docetaxel every 3 weeks for 6 cycles (CHAARTED (Sweeney et al. 2016) and STAMPEDE (James et al. 2016)). One study (GETUG-AFU15) which considered a dose of 75mg/m^2 of docetaxel delivered every 3 weeks for 9 cycles could not detect a difference in survival between the intervention and control group. The committee explained that docetaxel is a highly toxic chemotherapy treatment therefore it is not unexpected that prolonged use is not beneficial.

The committee considered the definition of ‘high-risk’ non-metastatic prostate cancer and agreed that (based on the inclusion criteria of the Stampede and GETUG-12 studies) for the purposes of these recommendations, high-risk disease meant one or more of the following:

- Stage T3/T4 or
- Gleason score 8-–10 or
- PSA greater than 40ng/ml

The committee also noted that this definition will be different from the one mentioned in the table on risk stratification for people with localised prostate cancer where high risk localised prostate cancer is defined as

- clinical stage ≥T2c or
- PSA >20ng/ml or
- Gleason score 8-10

This is because, the recommendation made here reflects the exact population included in the studies

When considering docetaxel in people with newly diagnosed high-risk non-metastatic prostate cancer, the benefits were not as clear as in those diagnosed with metastatic cancer. The evidence could not detect a difference in overall survival and prostate-specific survival between the intervention and control group. However, the evidence showed that clinical progression-free survival improved in those who received docetaxel compared with those who were on hormone therapy alone. As a result, the committee made a recommendation for clinicians to discuss the benefits and harms of docetaxel chemotherapy with those people who have been diagnosed with high-risk prostate cancer to arrive at a shared decision about docetaxel chemotherapy. The committee emphasised that this should be a joint decision taking into account the person's values and preferences.

Based on the evidence from 2 out of the 3 studies (STAMPEDE (James 2016), and TAX 3501 (Schweizer 2014)), the committee recommended that clinicians should use six 3-weekly cycles at a dose of 75mg/m^2. This dose was shown to prolong clinical progression free-survival in men with high-risk non-metastatic prostate cancer. Similar to the regimen in those with hormone-sensitive metastatic cancer this can be with or without daily prednisolone. Only 1 out of the 3 studies (STAMPEDE (James 2016) used daily prednisolone. Docetaxel chemotherapy was shown to be effective in improving clinical progression-free survival with or without daily prednisolone use.

Cost effectiveness and resource use

The committee reviewed the included economic evidence. It agreed that the included cost–utility analysis provided directly applicable evidence, as it drew its key evidence from a UK RCT (STAMPEDE). The committee noted some limitations of the analyses, particularly that they were reliant on substantial extrapolation from observed survival data, there had been no attempt to validate the model-based cost–utility analyses using the empirical findings of the RCT on which they were based, and they did not present the results of probabilistic sensitivity analyses in a way that enabled exploration. The committee understood that the degree of extrapolation is much greater in the non-metastatic population, where the model predicts a substantial lifetime survival advantage for people receiving docetaxel. Although this is a plausible finding, given the meaningful difference in progression-free survival observed in this group, an overall survival benefit has not yet been demonstrated in the trial data, and the visual fit of the modelled survival to that observed in the trial is poor. The authors acknowledge that a high degree of uncertainty remains around this aspect of the model, and conducted sensitivity analysis that attempted to simulate similar survival in the 2 arms. This showed that docetaxel remained cost effective because, even though they did not live any longer, the simulated population receiving docetaxel spent longer in the pre-progression state – which has higher quality of life. The committee concluded that the data were sufficient to underpin its recommendation that the benefits and harms of docetaxel should be discussed with people with non-metastatic disease, and treatment provided to people who choose it. However, it agreed that it was appropriate to consider the analysis as subject to potentially serious limitations, as future follow-up of the STAMPEDE RCT may lead to different cost-effectiveness conclusions, in this population.

In contrast, the modelled cost–utility analysis for people with metastatic hormone-sensitive disease was considered to be subject to minor limitations only. This is because the degree of extrapolation is much less (around 30% of participants remain alive, whereas only around 30% have died in the non-metastatic cohort). Moreover, the model finding that docetaxel is associated with overall survival benefit is borne out by the empirical data, in this instance.

The committee was therefore confident that the benefits outweighed the harms and costs associated with docetaxel in this population.

The committee noted that, across both populations, STAMPEDE had found that, in the first year of the trial, people receiving docetaxel had worse quality of life (EQ-5D) than people receiving standard care, to a degree that was small but statistically significant (mean difference −0.02 [95%CI: −0.03, −0.01]). The committee thought this was plausible, as docetaxel is associated with nontrivial toxicities, and it is recognised that its use trades off short-term adverse events against the potential for long-term gains in time to progression and survival.

The committee agreed that its recommendations would not have a significant resource impact. The best current estimates are that docetaxel is associated with net cost savings in the non-metastatic population, and that any small increase in costs in the metastatic cohort is clearly justified by substantial benefits. Docetaxel itself accounts for relatively little of any difference in costs between approaches, as it has become available in generic formulations in recent years.

1 Appendices

2 Appendix A – Review protocols

3 Review protocol for RQ5 - Docetaxel in hormone-sensitive locally advanced prostate cancer

ID	Field (based on PRISMA-P	Content
I	Review question	What is the most clinically- and cost-effective scheduling of docetaxel or added to standard treatment for the treatment of hormone-sensitive locally-advanced prostate cancer?
II	Type of review question	Intervention
III	Objective of the review	To determine the most effective scheduling of docetaxel added to standard treatment for the treatment of hormone-sensitive locally-advanced prostate cancer There are no existing recommendations on docetaxel in hormone sensitive locally-advanced prostate cancer.
IV	Eligibility criteria – population/disease/condition/issue/ domain	People with hormone-sensitive locally-advanced prostate cancer
V	Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Docetaxel added to standard treatment

VI	Eligibility criteria – comparator(s)/control or reference (gold) standard	• Placebo added to Standard treatment • Standard treatment alone

VII	Outcomes and prioritisation	• Overall survival
		• Progression free survival
		• Prostate-cancer-specific mortality
		• Treatment-related mortality
		• Metastasis-free survival
		• Health-related quality of life (for example: EORTC, EPIC instrument)
		• Number of severe adverse events
		  ○ sepsis,
		  ○ pancytopenia
		• Treatment discontinuation because of adverse events

VIII	Eligibility criteria – study design	RCTs Systematic reviews of RCTs
IX	Other exclusion criteria	Non-English language papers
X	Proposed sensitivity/sub-group analysis, or meta-regression	• Different schedules • Staging • Standard of care (radiotherapy, hormone therapy and surgery)
XI	Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until

		agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer
XII	Data management (software)	See appendix B below – section 1.3
XIII	Information sources – databases and dates	See appendix C of relevant chapter No date limits as this is a new question
XIV	Identify if an update	This is a new question. No question in previous guidelines on use of docetaxel or abiraterone in hormone-sensitive locally advanced prostate cancer. Linked recommendations from TA101 for hormone-relapsed prostate cancer: 1.5.11 Docetaxel is recommended, within its licensed indications, as a treatment option for men with hormone-refractory prostate cancer only if their Karnofsky performance-status score is 60% or more. **[2008]*** 1.5.12 It is recommended that treatment with docetaxel should be stopped: • at the completion of planned treatment of up to 10 cycles, or • if severe adverse events occur, or • in the presence of progression of disease as evidenced by clinical or laboratory criteria, or by imaging studies. **[2008]***

		1.5.13 Repeat cycles of treatment with docetaxel are not recommended if the disease recurs after completion of the planned course of chemotherapy. **[2008]***
XV	Author contacts	Guideline updates team
XVI	Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
XVII	Search strategy – for one database	For details please see appendix C of relevant chapter
XVIII	Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or H (economic evidence tables).
XIX	Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or H (economic evidence tables).
XX	Methods for assessing bias at outcome/study level	See Appendix B below – see section 1.4.1
XXI	Criteria for quantitative synthesis (where suitable)	See Appendix B below
XXII	Methods for analysis – combining studies and exploring (in)consistency	See Appendix B below – see section 1.4.2

XXIII	Meta-bias assessment – publication bias, selective reporting bias	See Appendix B below – see section 1.4.3 and 1.4.5
XXIV	Assessment of confidence in cumulative evidence	See Appendix B below - see section 1.4.3
XXV	Rationale/context – Current management	For details please see the introduction to the evidence review in the main file.
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the NICE Guideline Updates Team and chaired by Waqaar Shah in line with section 3 of Developing NICE guidelines: the manual. Staff from NICE undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
XXVII	Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
XXVIII	Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
XXIX	Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
XXX	PROSPERO registration number	N/A

Review protocol for RQ6 - Docetaxel in hormone-sensitive metastatic prostate cancer

ID	Field (based on PRISMA-P	Content
I	Review question	What is the most clinically- and cost-effective scheduling of docetaxel added to standard treatment for the treatment of hormone-sensitive metastatic prostate cancer? *New question – this question is looking at the off label use of docetaxel, please note there is a TA on the licensed use TA101*
II	Type of review question	Intervention
III	Objective of the review	To determine the most effective scheduling of docetaxel added to standard treatment for the treatment of hormone-sensitive metastatic prostate cancer There are no existing recommendations on docetaxel in hormone sensitive metastatic prostate cancer.
IV	Eligibility criteria – population/disease/condition/issue/ domain	People with hormone-sensitive metastatic prostate cancer (or within 3 months of starting hormone therapy)
V	Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Docetaxel added to standard treatment (standard treatment as defined by study)

VI	Eligibility criteria – comparator(s)/control	• Placebo added to Standard treatment or • Standard treatment alone

VII	Outcomes and prioritisation	• Overall survival
		• Progression free survival (defined by the studies)
		• Prostate-cancer-specific mortality
		• Health-related quality of life (for example: EORTC, EPIC instrument)
		• Number of severe adverse events
		  ○ sepsis,
		  ○ pancytopenia
		• Number of treatment discontinuations because of adverse events

VIII	Eligibility criteria – study design	• RCTs • Systematic reviews of RCTs
IX	Other inclusion exclusion criteria	Non-English language papers
X	Proposed sensitivity/sub-group analysis, or meta-regression	• Different schedules (doses and frequencies) • Placebo –controlled • Standard treatment controlled
XI	Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until

		agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer
XII	Data management (software)	See appendix B below – section 1.3
XIII	Information sources – databases and dates	See appendix C of relevant chapter
XIV	Identify if an update	This is a new clinical area, no previous question in previous updates. **Original question**: New question, no original question in guideline/. **Recommendations that may be affected:** No existing recommendations on docetaxel in hormone sensitive metastatic prostate cancer. However please **note** TA101 – "Docetaxel for the treatment of hormone-refractory metastatic prostate cancer" recommends: 1.1 Docetaxel is recommended, within its licensed indications, as a treatment option for men with hormone-refractory metastatic prostate cancer only if their Karnofsky performance-status score is 60% or more. 1.2 It is recommended that treatment with docetaxel should be stopped: • at the completion of planned treatment of up to 10 cycles, or • if severe adverse events occur, or

		• in the presence of progression of disease as evidenced by clinical or laboratory criteria, or by imaging studies. Repeat cycles of treatment with docetaxel are not recommended if the disease recurs after completion of the planned course of chemotherapy.
XV	Author contacts	Guideline updates team
XVI	Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
XVII	Search strategy – for one database	For details please see appendix C of relevant chapter
XVIII	Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or H (economic evidence tables).
XIX	Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or H (economic evidence tables).
XX	Methods for assessing bias at outcome/study level	See Appendix B below – see section 1.4.1
XXI	Criteria for quantitative synthesis (where suitable)	See Appendix B below
XXII	Methods for analysis – combining studies and exploring (in)consistency	See Appendix B below – see section 1.4.2

XXIII	Meta-bias assessment – publication bias, selective reporting bias	See Appendix B below – see section 1.4.3 and 1.4.5
XXIV	Assessment of confidence in cumulative evidence	See Appendix B below - see section 1.4.3
XXV	Rationale/context – Current management	For details please see the introduction to the evidence review in the main file.
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the NICE Guideline Updates Team and chaired by Waqaar Shah in line with section 3 of Developing NICE guidelines: the manual. Staff from NICE undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
XXVII	Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
XXVIII	Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
XXIX	Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
XXX	PROSPERO registration number	N/A

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Appendix B – Methods

Priority screening

Some of the reviews undertaken for this guideline made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened.

Research is currently ongoing as to what are the appropriate thresholds where reviewing of abstract can be stopped, assuming a defined threshold for the proportion of relevant papers it is acceptable to miss on primary screening. As a conservative approach until that research has been completed, the following rules were adopted during the production of this guideline:

- In every review, at least 50% of the identified abstract (or 1,000 records, if that is a greater number) were always screened.
- After this point, screening was only terminated if a pre-specified threshold was met for a number of abstracts being screened without a single new include being identified. This threshold was set according to the expected proportion of includes in the review (with reviews with a lower proportion of includes needing a higher number of papers without an identified study to justify termination), and was always a minimum of 250.
- A random 10% sample of the studies remaining in the database when the threshold were additionally screened, to check if a substantial number of relevant studies were not being correctly classified by the algorithm, with the full database being screened if concerns were identified.

As an additional check to ensure this approach did not miss relevant studies, the included studies lists of included systematic reviews were searched to identify any papers not identified through the primary search.

Incorporating published systematic reviews

For all review questions where a literature search was undertaken looking for a particular study design, systematic reviews containing studies of that design were also included. All included studies from those systematic reviews were screened to identify any additional relevant primary studies not found as part of the initial search.

Quality assessment

Individual systematic reviews were quality assessed using the ROBIS tool, with each classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.

- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.
- Low quality – It is possible that relevant and important studies have been missed by the review.

Each individual systematic review was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.
- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline (for example, some of the factors in the protocol only).
- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

Using systematic reviews as a source of data

If systematic reviews were identified as being sufficiently applicable and high quality, and were identified sufficiently early in the review process (for example, from the surveillance review or early in the database search), they were used as the primary source of data, rather than extracting information from primary studies. The extent to which this was done depended on the quality and applicability of the review, as defined in Table 5. When systematic reviews were used as a source of primary data, and unpublished or additional data included in the review which is not in the primary studies was also included. Data from these systematic reviews was then quality assessed and presented in GRADE/CERQual tables as described below, in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were cross-referenced to ensure none of the data had been double counted through this process.

Table 5: Criteria for using systematic reviews as a source of data

Quality	Applicability	Use of systematic review
High	Fully applicable	Data from the published systematic review were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review.
High	Partially applicable	Data from the published systematic review were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.

Quality	Applicability	Use of systematic review
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.

Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of studies for each outcome/predictor. For mean differences, where change from baseline data were reported in the trials/studies and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. These/All studies were assessed to ensure that baseline values were balanced across the treatment/comparison groups; if there were significant differences in important confounding variables at baseline these studies were not included in any meta-analysis and were reported separately.

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Cohort studies were quality assessed using the CASP cohort study checklist. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (Hedges' g).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method). Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis.

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Meta-analyses were performed in Cochrane Review Manager v5.3.

Minimal clinically important differences (MIDs)

The Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin. The committee did not identify any specific minimal important difference thresholds relevant to this guideline.

For standardised mean differences where no other MID was available, an MID of 0.2 was used, corresponding to the threshold for a small effect size initially suggested by Cohen et al. (1988). For relative risks where no other MID was available, a default MID interval for dichotomous outcomes of 0.8 to 1.25 was used. The line of no effect was specified by the committee as an MID for hazard ratios.

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review should make explicit the

committee's view of the expected clinical importance and relevance of the findings. In particular, this includes consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from RCTs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point. If non-RCT evidence was included for intervention-type systematic reviews then these were initially rated as either moderate quality (quasi-randomised studies) or low quality (cohort studies) and the quality of the evidence for each outcome was further downgraded or not from this point, based on the criteria given in Table 6

Table 6: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.

GRADE criteria	Reasons for downgrading quality
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if any of the following three conditions were met:

- Data from non-randomised studies showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data showing a dose-response gradient.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Publication bias was assessed in two ways. First, if evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts, trial protocols or trial records without accompanying published data), available information on these unpublished studies was reported as part of the review. Secondly, where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Evidence statements

Evidence statements for pairwise intervention data are classified in to one of four categories:

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect.
- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence could not demonstrate a meaningful difference.
- Situations where the data are consistent, at a 95% confidence level, with an effect in either direction (i.e. one that is not 'statistically significant') but the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no difference.
- In all other cases, we state that the evidence could not differentiate between the comparators.

Health economics

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline. There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 7.

Table 7 Applicability criteria

Level	Explanation
Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in Table 8.

Table 8 Methodological criteria

Level	Explanation
Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

Appendix C – Literature search strategies

Search summary

The search strategies were based on the review protocol provided. Docetaxel terms were taken from the British National Formulary (BNF), Martindale: The Complete Drug Reference and the electronic Medicines Compendium (eMC).

Clinical searches

Source searched for this review question:

- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley)
- Health Technology Assessment Database – HTA (Wiley)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)
- PubMed (NLM)

The clinical searches were conducted in October 2017

The MEDLINE search strategy is presented below. It was translated for use in all other databases.

Database: Ovid MEDLINE(R) 1946 to October Week 2 2017
1 exp Prostatic Neoplasms/
2 Prostatic Intraepithelial Neoplasia/
3 (prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump*)).tw.
4 PIN.tw.
5 or/1-4
6 Taxoids/
7 (Docetaxel* or Daxotel* or Docefrez* or Taxceus* or Taxoter* or Taxespira* or Texot*).tw.
8 or/6-7
9 5 and 8

Study design filters and limits

The MEDLINE systematic review (SR) and Randomized Controlled Trial (RCT) filters were appended to the review question above and are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

The MEDLINE SR and RCT filters are presented below.
Systematic Review
1 Meta-Analysis.pt.
2 Network Meta-Analysis/
3 Meta-Analysis as Topic/

The MEDLINE SR and RCT filters are presented below.
4 Review.pt.
5 exp Review Literature as Topic/
6 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw.
7 (review$ or overview$).ti.
8 (systematic$ adj5 (review$ or overview$)).tw.
9 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw.
10 ((studies or trial$) adj2 (review$ or overview$)).tw.
11 (integrat$ adj3 (research or review$ or literature)).tw.
12 (pool$ adj2 (analy$ or data)).tw.
13 (handsearch$ or (hand adj3 search$)).tw.
14 (manual$ adj3 search$).tw.
15 or/1-14
RCT
1 Randomized Controlled Trial.pt.
2 Controlled Clinical Trial.pt.
3 Clinical Trial.pt.
4 exp Clinical Trials as Topic/
5 Placebos/
6 Random Allocation/
7 Double-Blind Method/
8 Single-Blind Method/
9 Cross-Over Studies/
10 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.
11 (random$ adj3 allocat$).tw.
12 placebo$.tw.
13 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
14 (crossover$ or (cross adj over$)).tw.
15 or/1-14

1 An English language limit has been applied. Animal studies and certain publication types
2 (letters, historical articles, comments, editorials, news and case reports) have been excluded.

Health Economics search strategy

4 Economic evaluations and quality of life data.

5 Sources searched:

6 • NHS Economic Evaluation Database – NHS EED (Wiley) (legacy database)
7 • Health Technology Assessment (HTA Database)
8 • EconLit (Ovid)
9 • Embase (Ovid)
10 • MEDLINE (Ovid)
11 • MEDLINE In-Process (Ovid)

12 Search filters to retrieve economic evaluations and quality of life papers were appended to
13 population search terms in MEDLINE, MEDLINE In-Process and Embase to identify relevant
14 evidence and can be seen below.

15 An English language limit has been applied. Animal studies and certain publication types
16 (letters, historical articles, comments, editorials, news and case reports) have been excluded.

1 The economic searches were conducted in October 2017.

Health Economics filters

3

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

Economic evaluations

1 Economics/
2 exp "Costs and Cost Analysis"/
3 Economics, Dental/
4 exp Economics, Hospital/
5 exp Economics, Medical/
6 Economics, Nursing/
7 Economics, Pharmaceutical/
8 Budgets/
9 exp Models, Economic/
10 Markov Chains/
11 Monte Carlo Method/
12 Decision Trees/
13 econom$.tw.
14 cba.tw.
15 cea.tw.
16 cua.tw.
17 markov$.tw.
18 (monte adj carlo).tw.
19 (decision adj3 (tree$ or analys$)).tw.
20 (cost or costs or costing$ or costly or costed).tw.
21 (price$ or pricing$).tw.
22 budget$.tw.
23 expenditure$.tw.
24 (value adj3 (money or monetary)).tw.
25 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26 or/1-25

Quality of life

1 "Quality of Life"/
2 quality of life.tw.
3 "Value of Life"/
4 Quality-Adjusted Life Years/
5 quality adjusted life.tw.
6 (qaly$ or qald$ or qale$ or qtime$).tw.
7 disability adjusted life.tw.
8 daly$.tw.
9 Health Status Indicators/
10 (sf36 or sf 36 or 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).tw.
11 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

14 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15 (euroqol or euro qol or eq5d or eq 5d).tw.
16 (qol or hql or hqol or hrqol).tw.
17 (hye or hyes).tw.
18 health$ year$ equivalent$.tw.
19 utilit$.tw.
20 (hui or hui1 or hui2 or hui3).tw.
21 disutili$.tw.
22 rosser.tw.
23 quality of wellbeing.tw.
24 quality of well-being.tw.
25 qwb.tw.
26 willingness to pay.tw.
27 standard gamble$.tw.
28 time trade off.tw.
29 time tradeoff.tw.
30 tto.tw.
31 or/1-30

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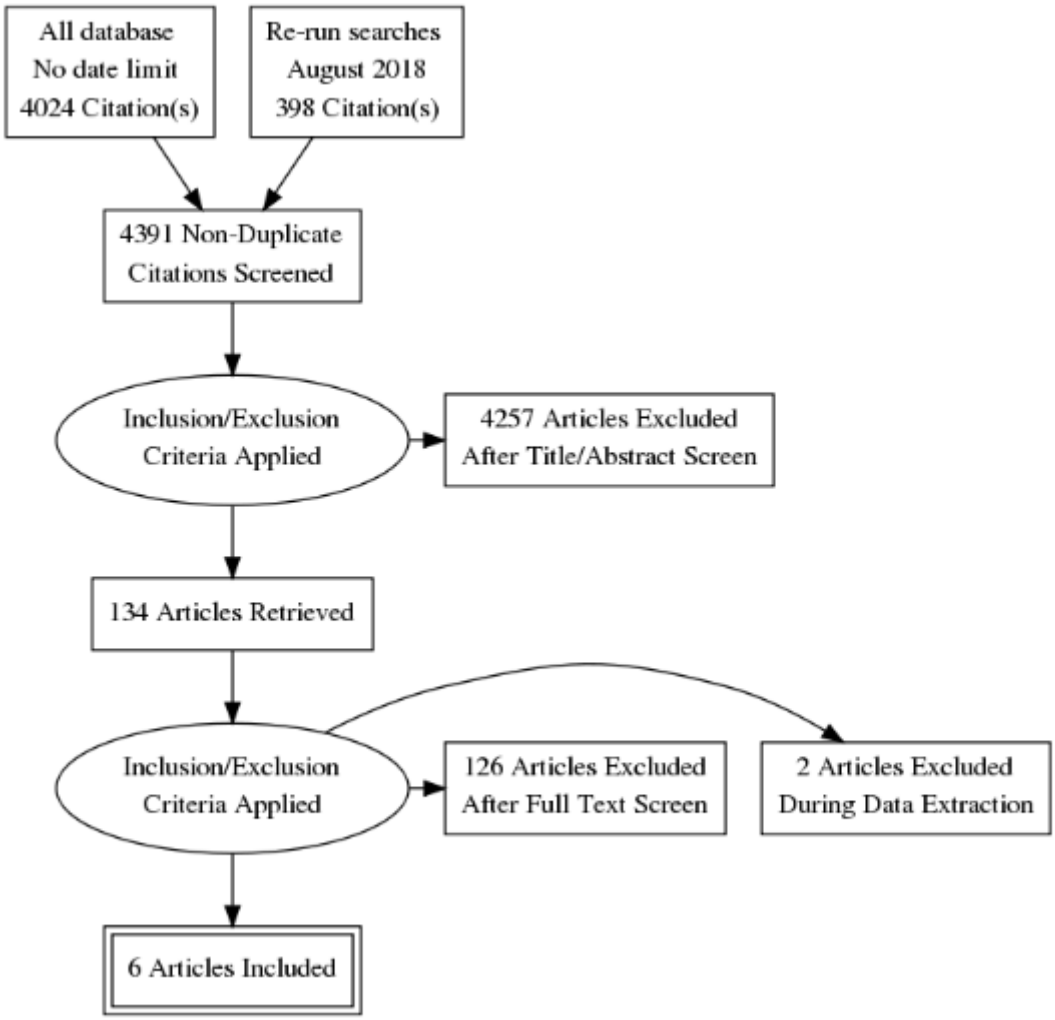
Appendix D – Clinical evidence study selection



2

Appendix E – Clinical evidence tables

Hormone sensitive high risk prostate cancer

Short Title	Title	New column	New column
Fizazi (2015)	Androgen deprivation therapy plus docetaxel and estramustine versus androgen deprivation therapy alone for high-risk localised prostate cancer (GETUG 12): a phase 3 randomised controlled trial	**Study type** Randomised controlled trial **Study details** Study location France (26 centres) Study setting Hospitals Study dates November 2002 and December 2006 Sources of funding Ligue Contre le Cancer, Sanofi-Aventis, AstraZeneca, Institut du Cancer **Inclusion criteria** Histologically confirmed adenocarcinoma and radiologically proved metastases With at least one of the following - Gleason score of 8 or greater, stage T3 or T4 disease, serum PSA concentration of 20ng/ml or more, or pathological node-positive disease No evidence of metastases on bone scan and abdominopelvic CT scan within the past 6 months **Exclusion criteria** Previous treatment of prostate cancer **Sample characteristics** Sample size 413 patients Split between study groups	**Random sequence generation** Unclear risk of bias randomisation was carried out centrally, however it is unclear whether or not they had random sequence generation **Allocation concealment** High risk of bias Neither patients nor investigators were masked to treatment allocation - authors state that an intravenous placebo would have been invasive especially if a central venous access was used and many patients knew when they received chemo due to the side effects **Blinding of participants and personnel** High risk of bias As above **Blinding of outcome assessment** High risk of bias Unlikely as study was open label, the patients also self-completed the quality of life questionnaire **Incomplete outcome data** Low risk of bias None identified **Selective reporting** Low risk of bias

Short Title	Title	New column	New column
		Mean age (SD) Median age (range) = 63 years (IQR 47-77) **Interventions** ADT alone goserelin 10.8mg every 3 months via subcutaneous injection ADT and Docetaxel and Estramustine Docetaxel was given on day 2 - at a dose of 70mg/m2 in a 1 hour intravenous infusion, repeated every 3 weeks for 4 cycles **Outcome measure(s)** Overall survival Relapse-free survival Defined as biochemical failure, onset of metastases on imaging, proven local relapse, use of salvage treatment and death	None identified **Other sources of bias** Unclear risk of bias One patient had metastatic cancer and 4 with other comorbidities were included in the study, despite exclusion criteria **Overall risk of bias** High Due to open label status of the study and lack of adherence to inclusion/exclusion criteria **Directness** Directly applicable
James (2016)	Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial	**Study type** Randomised controlled trial **Study details** Study location United Kingdom Study setting Hospital Study dates October 2005 and March 2013 Duration of follow-up 6 weekly to 6 months, 12 weekly to 2 years, 6 monthly to 5 years then annually Sources of funding Cancer Research Uk, MedicalResearch Council, Novartis, Sanofi-Aventis, Pfizer, Janssen, Astellas, NIHR Clinical Research Network, Swiss Group for Clinical Cancer	**Random sequence generation** Low risk of bias Patients were randomised centrally using a computerised algorithm, developed and maintained by the trials unit. **Allocation concealment** High risk of bias Authors state ".Masking to treatment allocation was considered impracticable and of limited value given the primary outcome measure" **Blinding of participants and personnel** High risk of bias As above

Short Title	Title	New column	New column
		Research **Inclusion criteria** Newly diagnosed with prostate cancer- as metastatic, node positive or high-risk locally advanced (with at least two of T3/4, Gleason score of 8-10, and prostate-specific >/= 40ng/ml) Or previously treated with radical surgery, radiotherapy or both and relapsing with high-risk features No age restrictions **Exclusion criteria** severe cardiac disease **Sample characteristics** Sample size 1776 patients Split between study groups Mean age (SD) Median age (range) = 65 years (40-84) **Interventions** Docetaxel and standard of care 75mg/m2 was given for six 3-weekly cycles with 10mg of prednisolone daily and standard premedication before each injection. **Standard of care** Hormone therapy for at least 2 years with gonadotropin-releasing hormone agonists or antagonists or only between 2006 and 2011 for patients with non-metastatic disease, oral anti-androgens alone. Radiotherapy was encouraged for patients with N0M0 disease until November 2011. **Outcome measure(s)** Overall survival	**Blinding of outcome assessment** Low risk of bias Authors state "Cause of death was determined by masked central review..." **Incomplete outcome data** Low risk of bias None identified **Selective reporting** Low risk of bias None identified **Other sources of bias** Unclear risk of bias the exclusion criteria mentioned that participants had to be newly diagnosed with prostate cancer, 6% of participants had recurrent Prostate cancer **Overall risk of bias** Moderate Due to lack of allocation concealment and blinding to personnel and participants **Directness** Directly applicable

Short Title	Title	New column	New column
		Failure-free survival Time from randomisation to 1st evidence of at least one of the following - biochemical failure, progression either locally, in lymph nodes or in distant metastases or death from prostate cancer	
Schweizer (2013)	Adjuvant leuprolide with or without docetaxel in patients with high-risk prostate cancer after radical prostatectomy (TAX-3501): important lessons for future trials	**Study type** Randomised controlled trial **Associated studies** *Vale C L, Burdett S, Rydzewska L H. M, Albiges L, Clarke N W, Fisher D, Fizazi K, Gravis G, James N D, Mason M D, Parmar M K. B, Sweeney C J, Sydes M R, Tombal B, and Tierney J F (2016) Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: A systematic review and meta-analyses of aggregate data. The Lancet Oncology 17(2), 243-256* **Study details** Study location 108 countries including 45 centres in Europe **Study setting** Hospital Study dates December 2005 and September 2007 Duration of follow-up median follow up 3.4 years **Sources of funding** Sanofi **Inclusion criteria** Histologically confirmed adenocarcinoma and radiologically proved metastases ECOG performance greater than 1	**Random sequence generation** Unclear risk of bias This study was a randomised control trial, however no details on sequence generation was provided **Allocation concealment** Unclear risk of bias No details provided **Blinding of participants and personnel** Unclear risk of bias No details provided **Blinding of outcome assessment** Unclear risk of bias Unclear - though not critical as endpoints were objective - overall survival and progression free survival **Incomplete outcome data** Low risk of bias **Selective reporting** Unclear risk of bias Authors did not report on overall survival, however data for this review extracted from a MRC UCL systematic review article **Other sources of bias** Low risk of bias

Short Title	Title	New column	New column
		Life expectancy greater than 1 Undergone radical prostatectomy <120 days before randomisation Deemed high risk of recurrence Post-operative PSA levels <0.2ng/ml at least 30 days after RP and within 7 days of randomisation Normal hematologic, renal and hepatic function Normal serum testosterone >150ng/dl **Sample characteristics** Sample size 228 patients Split between study groups **Interventions** Docetaxel and leuprolide 75mg/m2 intravenously over 1 hour repeated every 3 weeks for a total of cycles Leuprolide alone 22.5mg was given subcutaneously every 3 months for a total of 18 months of treatment **Outcome measure(s)** Overall survival Clinical progression-free survival; cPFS Safety	none identified **Overall risk of bias** High the authors did not provide any details on sequence generation, the study was an open label study **Directness** Directly applicable

1 **Table 9: Adverse events - high risk prostate cancer**

Study	Authors description of adverse events	Number (%)
TAX 3501 Schweizer 2013	At least 1 adverse event considered to be possibly drug related. The majority were grade 1 or grade 2 , grade 3 and 4 were uncommon reported to have occurred in 21 patients	118/138 patients (84%)
GETUG 12 Fizazi 2012	Only 5 patients developed a neutropenic fever. No patient required blood or platelet transfusion. There was no toxicity-related death. No patient in the ADT arm developed grade 3-4 toxicity during the 3 first months	

Study	Authors description of adverse events	Number (%)
STAMPEDE James 2016 (also applies to the metastatic prostate cancer)	Only 5 patients had grade 5 adverse events and 298 patients had grade 3-5 adverse events in the group that received docetaxel treatment. The most frequent adverse events were endocrine disorder (10% of the intervention group), febrenile neutropenia (15% of the intervention group) and neutropenia (12% of the intervention group)	

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2 **Hormone-sensitive metastatic prostate cancer**

Short Title	Title	New column	New column
Gravis (2013)	Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial	**Study type** Randomised controlled trial **Associated studies** Gravis G, Boher J M, Joly F, Soulie M, Albiges L, Priou F, Latorzeff I, Delva R, Krakowski I, Laguerre B, Rolland F, Theodore C, Deplanque G, Ferrero J M, Culine S, Mourey L, Beuzeboc P, Habibian M, Oudard S, and Fizazi K (2016) Androgen Deprivation Therapy (ADT) Plus Docetaxel Versus ADT Alone in Metastatic Non castrate Prostate Cancer: Impact of Metastatic Burden and Long-term Survival Analysis of the Randomized Phase 3 GETUG-AFU15 Trial. European Urology 70(2), 256-262 **Study details** Study location 29 Centres in France and 1 centre in Belgium Study setting Hospital Study dates	**Random sequence generation** Low risk of bias Randomisation was done by a clinical research organisation and was centralised nationally. **Allocation concealment** High risk of bias Patients, physicians, and data analysts were not masked to treatment allocation **Blinding of participants and personnel** High risk of bias Open label study **Blinding of outcome assessment** High risk of bias Open label study **Incomplete outcome data** Low risk of bias

Short Title	Title	New column	New column
		Oct 18, 2004, and Dec 31, 2008 Duration of follow-up Median follow-up 6 years, 11 months **Sources of funding** French Health Ministry and Institut National du Cancer (PHRC), Sanofi -Aventis, AstraZeneca, and Amgen **Inclusion criteria** Aged more than 18 years Histologically confirmed adenocarcinoma and radiologically proved metastases Karnofsky score of at least 70%; A life expectancy of at least 3 months Adequate hepatic, haematological and renal function **Exclusion criteria** Previous chemotherapy for metastatic disease severe cardiac disease Had surgical castration before metastatic disease occurred had peripheral neuropathy (at least grade 2) A history of another cancer in the past 5 years **Sample characteristics** Sample size 385 patients Split between study groups %female all male - prostate cancer Mean age (SD) ADT plus docetaxel - 63(57-68) ADT alone - 64(58-70) **Interventions** ADT and Docetaxel patients received 75 mg/m² intravenous docetaxel in a 250 cm³ 5% glucose solution in the course of 1 h on the	none identified **Selective reporting** Low risk of bias none identified **Overall risk of bias** Moderate Patients, physicians, and data analysts were not masked to treatment allocation. the study was an open label study, however as the primary outcomes are subjective the study was rated as moderate risk of bias **Directness** Directly applicable

Short Title	Title	New column	New column
		first day of each 21-day cycle. Treatment with docetaxel continued for up to nine cycles on the basis of the median exposure reported in the TAX 327 trial, ADT alone **Outcome measure(s)** Overall survival Clinical progression-free survival; cPFS biochemical progression-free survival; bPFS	
James (2016)	Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial	**Study type** Randomised controlled trial **Study details** Study setting Hospital **Study dates** October 2005 and March 2013 Duration of follow-up 6 weekly to 6 months, 12 weekly to 2 years, 6 monthly to 5 years then annually (Median follow up – 3 years, 6 months) **Sources of funding** Cancer Research Uk, MedicalResearch Council, Novartis, Sanofi-Aventis, Pfizer, Janssen, Astellas, NIHR Clinical Research Network, Swiss Group for Clinical Cancer Research **Inclusion criteria** Newly diagnosed with prostate cancer- as metastatic, node positive or high-risk locally advanced (with at least two of T3/4, Gleason score of 8-10, and prostate-specific >/= 40ng/ml) Or previously treated with radical surgery, radiotherapy or both and relapsing with high-risk features	**Random sequence generation** Low risk of bias Patients were randomised centrally using a computerised algorithm, developed and maintained by the trials unit. **Allocation concealment** High risk of bias Authors state "..Masking to treatment allocation was considered impracticable and of limited value given the primary outcome measure" **Blinding of participants and personnel** High risk of bias As above **Blinding of outcome assessment** Low risk of bias Authors state "Cause of death was determined by masked central review..." **Incomplete outcome data** Low risk of bias None identified

Short Title	Title	New column	New column
		No age restrictions **Exclusion criteria** severe cardiac disease **Sample characteristics** Sample size 1776 patients Split between study groups Mean age (SD) Median age (range) = 65 years (40-84) **Interventions** Docetaxel and standard of care 75mg/m2 was given for six 3-weekly cycles with 10mg of prednisolone daily and standard premedication before each injection. Standard of care Hormone therapy for at least 2 years with gonadotropin-releasing hormone agonists or antagonists or only between 2006 and 2011 for patients with non-metastatic disease, oral anti-androgens alone. Radiotherapy was encouraged for patients with N0M0 disease until November 2011. Outcome measure(s) Overall survival Failure-free survival Time from randomisation to 1st evidence of at least one of the following - biochemical failure, progression either locally, in lymph nodes or in distant metastases or death from prostate cancer	**Selective reporting** Low risk of bias None identified **Other sources of bias** Unclear risk of bias the exclusion criteria mentioned that participants had to be newly diagnosed with prostate cancer, 6% of participants had recurrent Prostate cancer **Overall risk of bias** Moderate No details were provided on sequence generation and blinding, however as the primary outcomes are subjective the study was rated as moderate risk of bias **Directness** Directly applicable
Sweeney (2015)	Chemohormonal therapy in metastatic	**Study type** Randomised controlled trial	**Random sequence generation** High risk of bias The study was randomised however no details

Short Title	Title	New column	New column
	hormone-sensitive prostate cancer	**Study details** Study location Study setting Hospitals **Study dates** July, 2006– November, 2012 Duration of follow up Median follow-up 2 years, 5 months Sources of funding National cancer institut, National Institutes of Health, Department of Health and Human Services and by grants from the Public health services, Sanofi provided the docetaxel and grant to ECOG-ACRIN **Inclusion criteria** Pathological disease of prostate cancer or dora clinical scenario consistent with prostate cancer elevated PSA Radiologic evidence of metastatic disease ECOG performance score of 0, 1, 2 Planned use of combined androgen blockade for more than 30 days or agents approved for prevention of skeletal related events in castration disease (zoledronic acid or denosumab) **Exclusion criteria** None reported **Sample characteristics** Sample size 790 patients Split between study groups Mean age (SD) Not provided - median (range) =64years (36-91)	provided on random sequence generation **Allocation concealment** Unclear risk of bias no details provided **Blinding of participants and personnel** Unclear risk of bias No details provided **Blinding of outcome assessment** Unclear risk of bias no details provided **Incomplete outcome data** Low risk of bias none identified **Selective reporting** Low risk of bias none identified **Other sources of bias** Low risk of bias none identified **Overall risk of bias** Moderate No details were provided on sequence generation and blinding, however as the primary outcomes are subjective the study was rated as moderate risk of bias **Directness** Directly applicable

Short Title	Title	New column	New column
		Interventions ADT and Docetaxel 75mg/m2 every 3 weeks for 6 cycles ADT alone **Outcome measure(s)** Overall survival Clinical progression-free survival; cPFS Time to castration-resistant prostate cancer	

Table 10: Adverse events - Metastatic prostate cancer

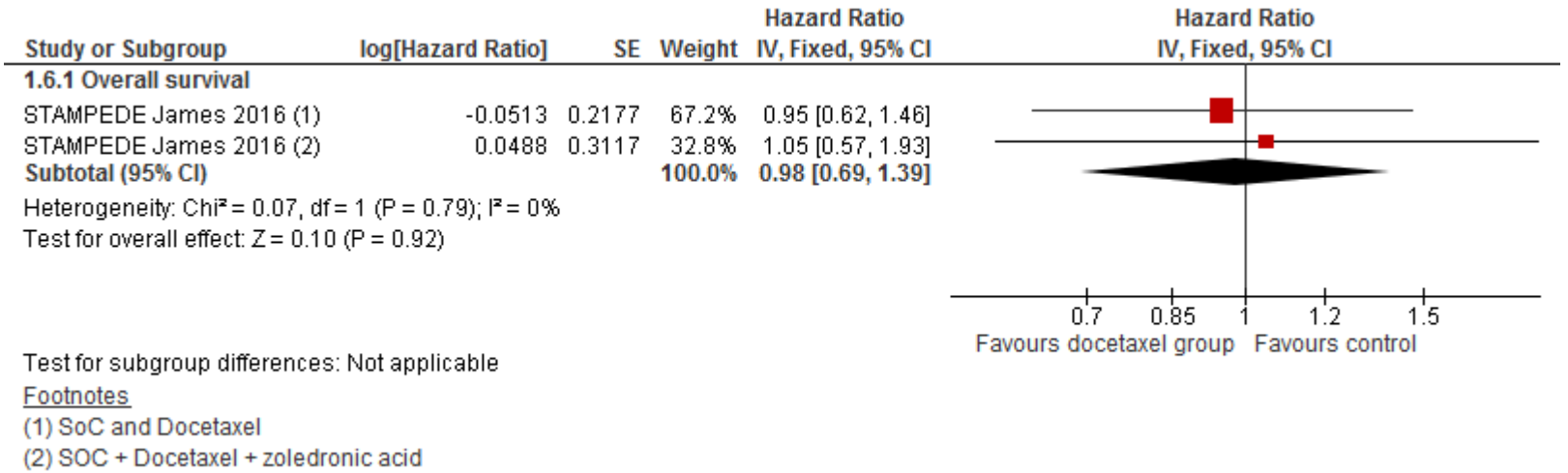
Study	Authors description of adverse events	Number (%)
CHAARTED Sweeney 2016	Only docetaxel group was reported - 1 patient had a grade 5 adverse event. 111 patients had grade 3-4 adverse events. The most frequent adverse events were neutropenia (12.1%), febrile neutropenia (6.1%) and fatigue 4.1%	111/390 (28%)
GETUG-15 Gravis 2013	2 patients had grade 5 adverse events. It is unclear how many patients had at least one grade 3-4 adverse event. The most frequent adverse events at grade 3-5 were neutropenia (32%, febrile neutropenia (7%), erectile dysfunction (8%) and decreased lobido (6%)	
STAMPEDE James 2016 (also applies to the locally advanced prostate cancer)	5 patients had grade 5 adverse events and 298 patients had grade 3-5 adverse events in the group that received docetaxel treatment. The most frequent adverse events were endocrine disorder (10% of the intervention group), febrenile neutropenia (15% of the intervention group) and neutropenia (12% of the intervention group)	

1

Appendix F – Forest plots

Docetaxel and Hormone-sensitive high risk prostate cancer

Overall survival



Test for subgroup differences: Not applicable

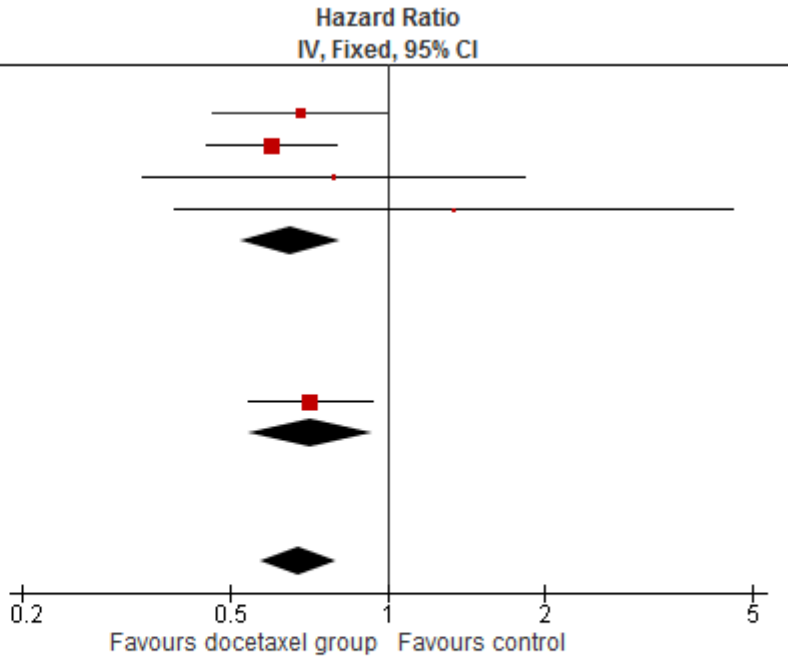
Footnotes

(1) SoC and Docetaxel

(2) SOC + Docetaxel + zoledronic acid

Clinical progression-free survival by dose

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
1.4.1 75mg/m2 every 3 weeks for a total of 6 cycles				
STAMPEDE James 2016 (1)	-0.3857	0.1994	19.2%	0.68 [0.46, 1.01]
STAMPEDE James 2016 (2)	-0.5108	0.1468	35.5%	0.60 [0.45, 0.80]
TAX 3501 Schweizer 2014 (3)	-0.2357	0.4302	4.1%	0.79 [0.34, 1.84]
TAX 3501 Schweizer 2014 (4)	0.2927	0.6297	1.9%	1.34 [0.39, 4.60]
Subtotal (95% CI)			**60.8%**	**0.65 [0.52, 0.81]**
Heterogeneity: Chi² = 1.87, df = 3 (P = 0.60); I² = 0%				
Test for overall effect: Z = 3.81 (P = 0.0001)				
1.4.2 70mg/m2 every 3 weeks for 4 cycles				
GETUG-12 Fizazi 2015	-0.3425	0.1396	39.2%	0.71 [0.54, 0.93]
Subtotal (95% CI)			**39.2%**	**0.71 [0.54, 0.93]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.45 (P = 0.01)				
Total (95% CI)			**100.0%**	**0.67 [0.57, 0.80]**
Heterogeneity: Chi² = 2.10, df = 4 (P = 0.72); I² = 0%				
Test for overall effect: Z = 4.50 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.22, df = 1 (P = 0.64), I² = 0%				



Footnotes

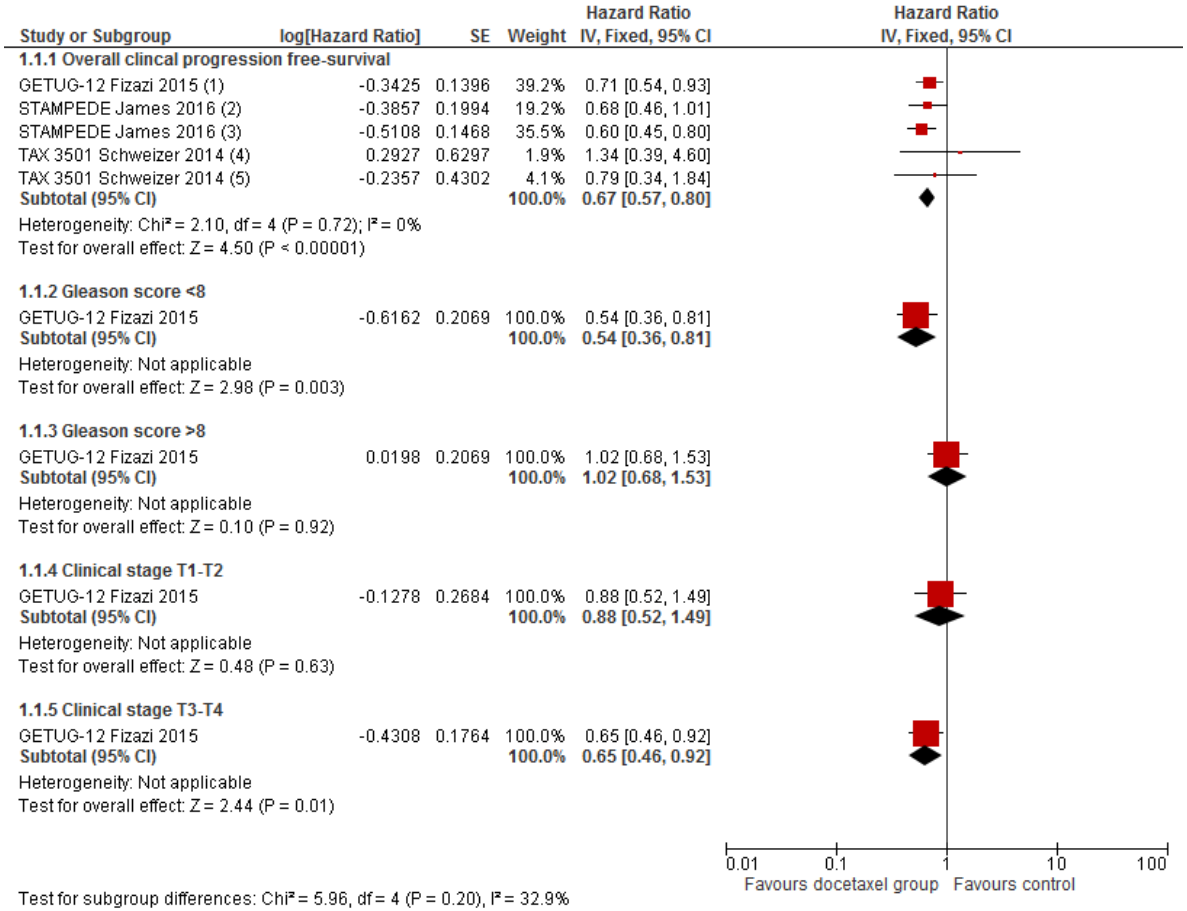
(1) SOC + Docetaxel + zoledronic acid

(2) SoC and Docetaxel

(3) immediate therapy group

(4) Hormonal therapy and docetaxel deffered therapy group

Overall Clinical progression-free survival and by high risk disease criterion

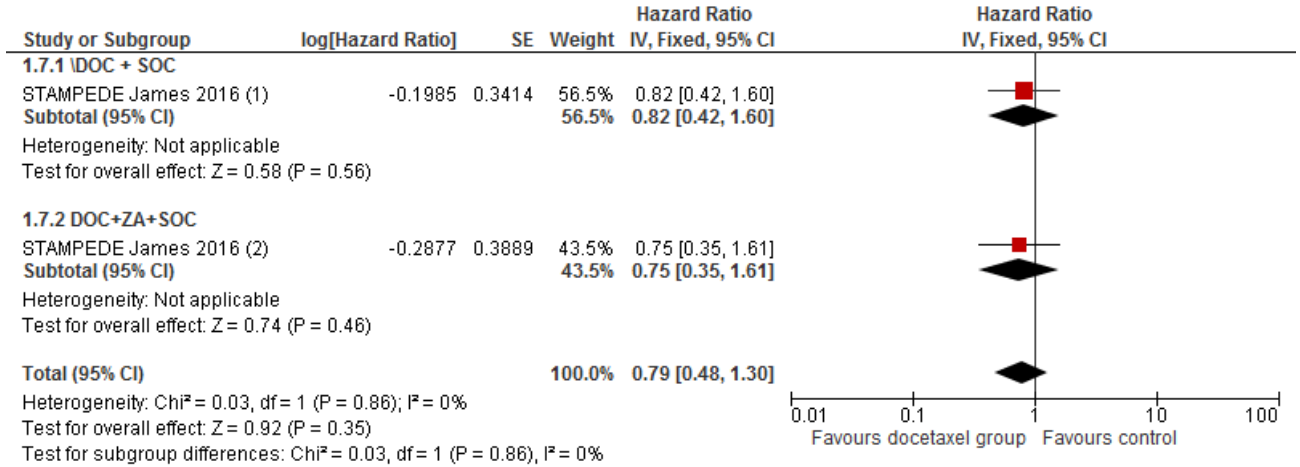


Test for subgroup differences: Chi² = 5.96, df = 4 (P = 0.20), I² = 32.9%

Footnotes

(1) Adt and docetaxel and estramustine versus DE alone, defined as relapse-free survival
(2) SOC + Docetaxel + zoledronic acid, defined as failure free survival
(3) SoC and Docetaxel, defined as failure free survival
(4) Hormonal therapy and docetaxel deffered therapy group, extracted from Vale 2016
(5) immediate therapy group, extracted from Vale 2016

Prostate cancer-specific survival

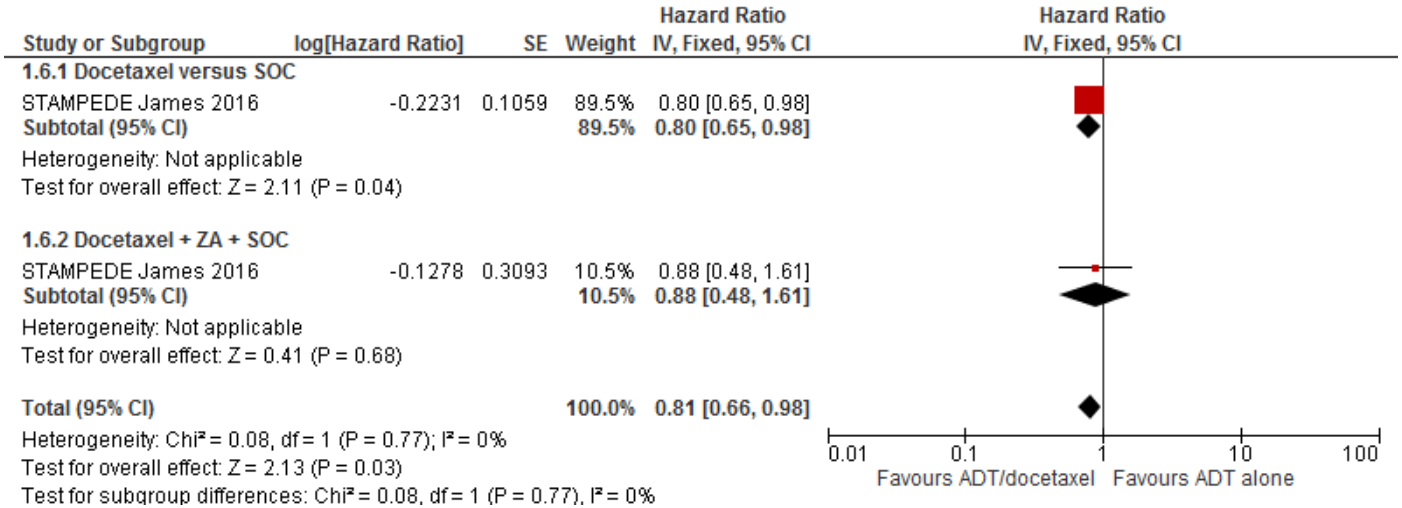


Footnotes

(1) SoC and Docetaxel

(2) SOC + Docetaxel + zoledronic acid

1 **Prostate cancer specific survival**



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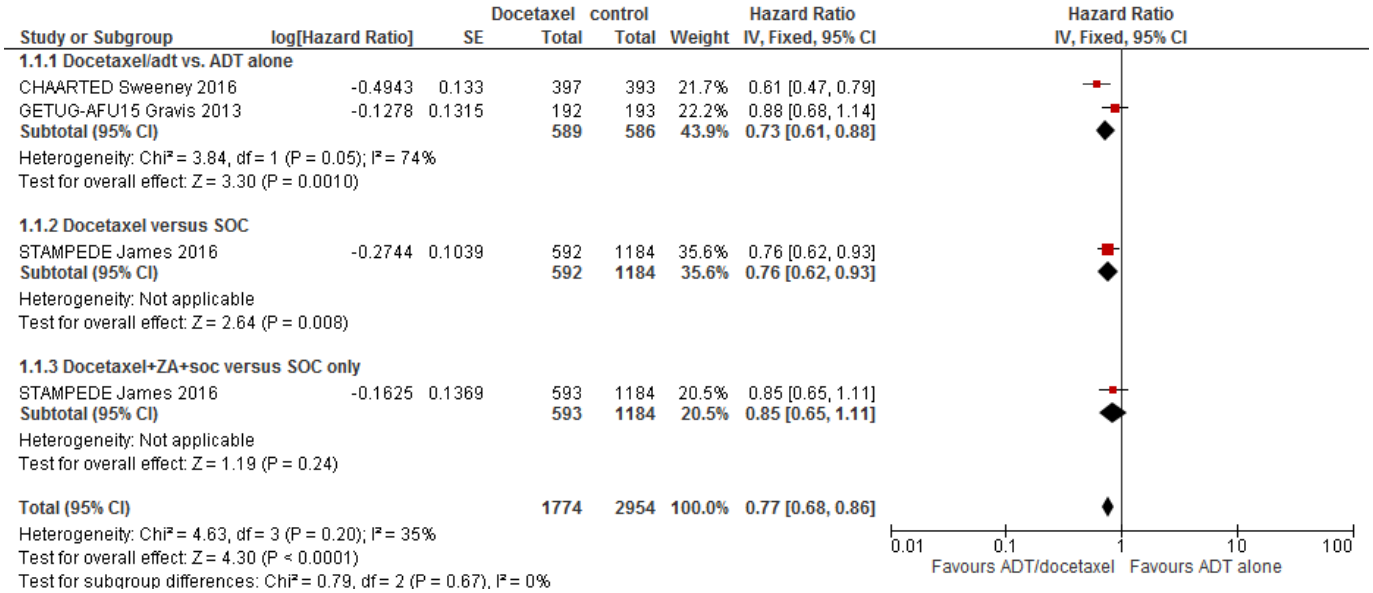
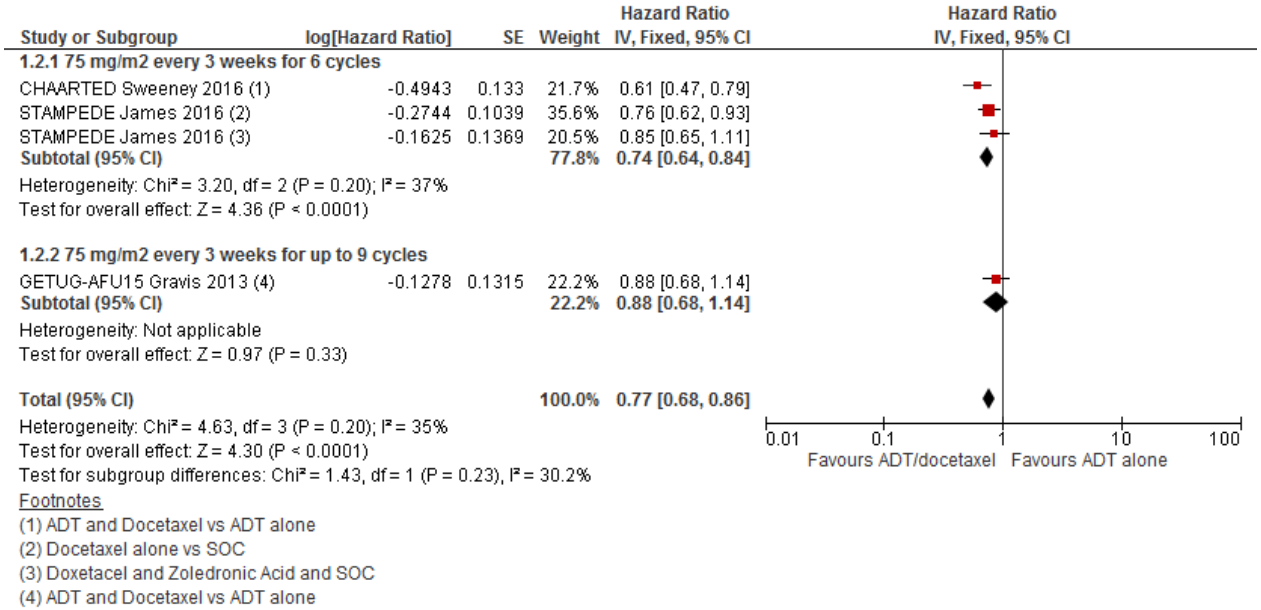
Docetaxel and Hormone sensitive metastatic prostate cancer

Overall survival



Overall survival stratified by dose



Footnotes

(1) ADT and Docetaxel vs ADT alone

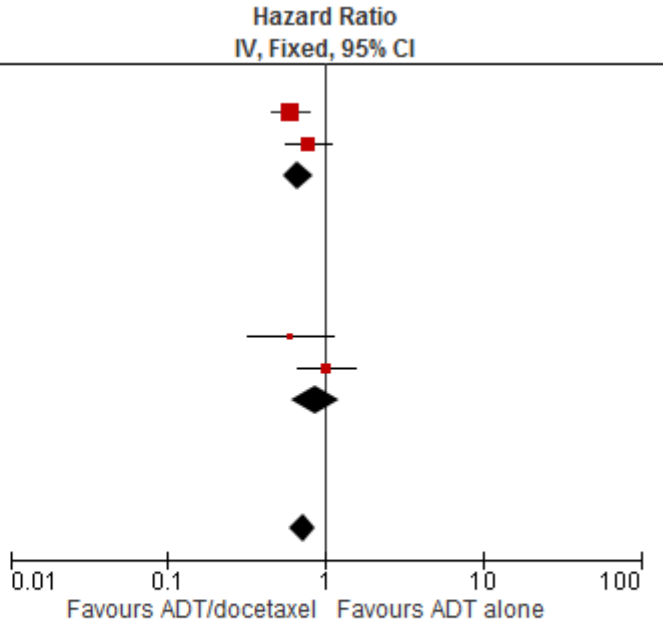
(2) Docetaxel alone vs SOC

(3) Doxetacel and Zoledronic Acid and SOC

(4) ADT and Docetaxel vs ADT alone

Overall survival by high volume or low volume disease

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
1.3.1 High volume disease				
CHAARTED Sweeney 2016 (1)	-0.5108	0.1468	41.1%	0.60 [0.45, 0.80]
GETUG-AFU15 Gravis 2013	-0.2485	0.1691	31.0%	0.78 [0.56, 1.09]
Subtotal (95% CI)			**72.1%**	**0.67 [0.54, 0.83]**
Heterogeneity: Chi² = 1.37, df = 1 (P = 0.24); I² = 27%				
Test for overall effect: Z = 3.59 (P = 0.0003)				
1.3.2 Low volume disease				
CHAARTED Sweeney 2016 (2)	-0.5108	0.3207	8.6%	0.60 [0.32, 1.12]
GETUG-AFU15 Gravis 2013	0.0198	0.2144	19.3%	1.02 [0.67, 1.55]
Subtotal (95% CI)			**27.9%**	**0.87 [0.61, 1.23]**
Heterogeneity: Chi² = 1.89, df = 1 (P = 0.17); I² = 47%				
Test for overall effect: Z = 0.81 (P = 0.42)				
Total (95% CI)			**100.0%**	**0.72 [0.60, 0.87]**
Heterogeneity: Chi² = 4.73, df = 3 (P = 0.19); I² = 37%				
Test for overall effect: Z = 3.48 (P = 0.0005)				
Test for subgroup differences: Chi² = 1.46, df = 1 (P = 0.23), I² = 31.7%				

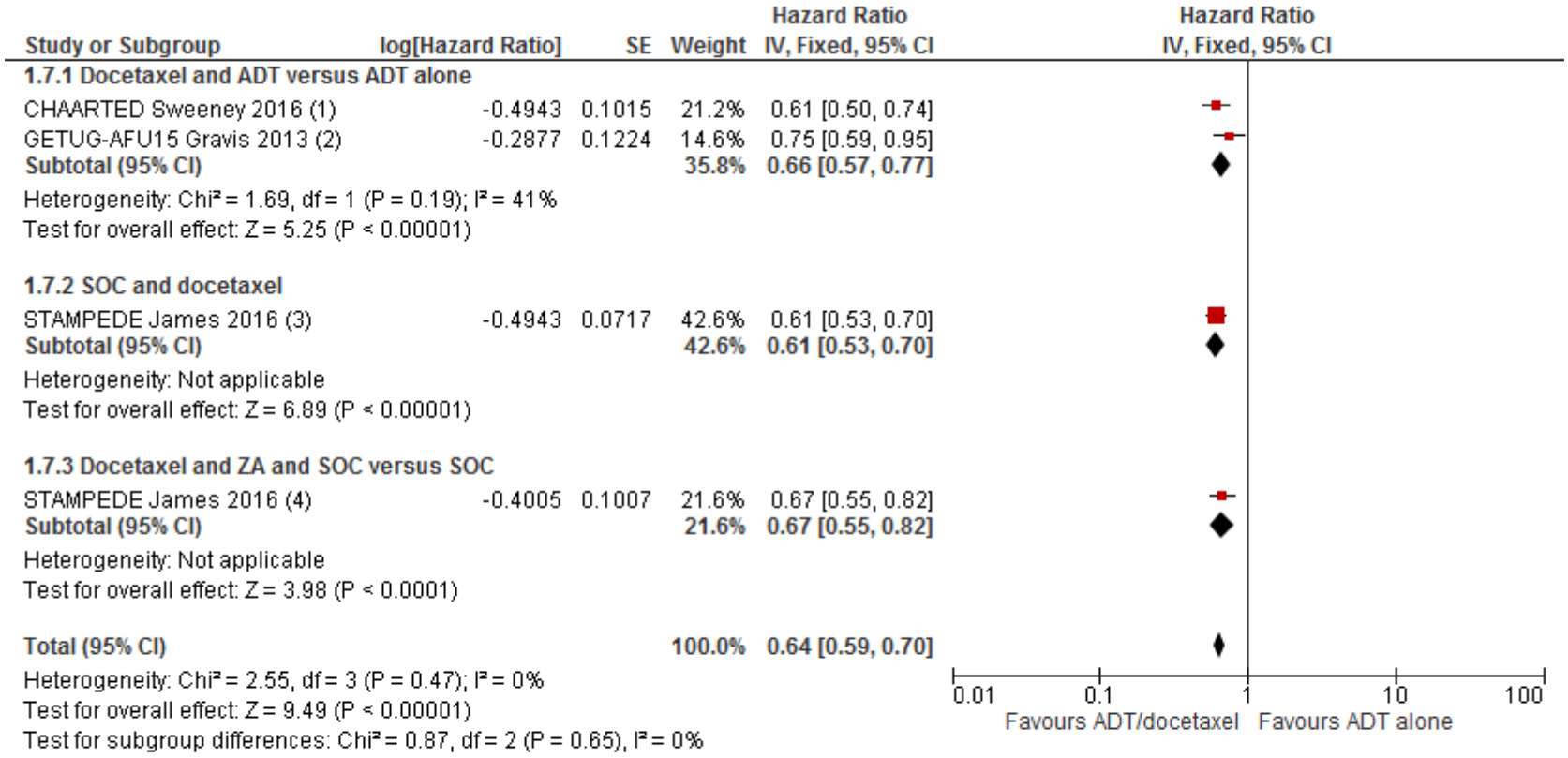


Footnotes

(1) high volume disease defined as the presence of visceral metastases or at least 4 bone lesions

(2) not meeting the HVD criteria

Clinical progression free survival



Footnotes

(1) defined by increasing symptoms of bone metastases; according to the Response Evaluation Criteria in Solid tumours, clinical deterioration due to...

(2) defined as time to clinical progression or death

(3) Failure-free survival - Biochemical failure, progression either locally, in lymph nodes or in distant mets, or death

(4) Failure-free survival - Biochemical failure, progression either locally, in lymph nodes or in distant mets, or death

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Appendix G – GRADE tables

Hormone-sensitive high risk prostate cancer

3 Docetaxel (combined with estramustine, zoledronic acid or ADT) versus Standard of Care (hormone therapy or ADT)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Overall survival– HR <1 favours docetaxel group										
1 study STAMPEDE James 2016	RCTs	1190	HR 0.98 (0.69, 1.39)	-	-	Not serious	Not serious	Not serious	Serious[1]	Moderate
Clinical progression-free survival– HR <1 favours docetaxel group										
3 studies STAMPEDE James 2016* TAX 3501 Schweizer 2014** GETUG-12 Fizazi 2015***	RCTs	1791	HR 0.67 (0.57, 0.80)	-	-	Not serious	Not serious	Not serious	Not serious	High
Clinical progression-free survival by dose 75mg/m2 every 3 weeks for a total of 6 cycles - HR <1 favours docetaxel group										
2 studies STAMPED James 2016 TAX 3501 Schweizer 2014	RCTs	1378	HR 0.65 (0.52, 0.81)	-	-	Not serious	Not serious	Not serious	Not serious	High

70mg/m2 every 3 weeks for a total of 4 cycles - HR <1 favours docetaxel group										
1 study GETUG-12 Fizazi 2015	RCTs	413	HR 0.71 (0.54, 0.93)	-	-	Not serious	Not serious	Not serious	Not serious	High
Clinical progression-free survival by criterion for high risk disease Gleason score <8- HR <1 favours docetaxel group										
1 study GETUG-12 Fizazi 2015	RCTs	238	HR 0.54 (0.36, 0.81)	-	-	Not serious	Not serious	Not serious	Not serious	High
Gleason score >8- HR <1 favours docetaxel group										
1 study GETUG-12 Fizazi 2015	RCTs	175	HR 1.02 (0.68, 1.53)	-	-	Not serious	Not serious	Not serious	Serious[1]	Moderate
Clinical stage T1-T2										
1 study GETUG-12 Fizazi 2015	RCTs	134	HR 0.88 (0.52, 1.49)	-	-	Not serious	Not serious	Not serious	Serious[1]	Moderate
Clinical stage T3-T4										
1 study GETUG-12 Fizazi 2015	RCTs	244	HR 0.65 (0.46, 0.92)	-	-	Not serious	Not serious	Not serious	Not serious	High
All cause-mortality – RR < 1 favours docetaxel group										
1 study GETUG-12 Fizazi 2015	RCT	413	RR 0.85 (0.59, 1.23)	12 people per 100	10 people per 100 (from 7 fewer to 15 more)	Not serious	Not serious	Not serious	Serious[2]	Moderate
Number of patients who developed metastases – RR < 1 favours docetaxel group										
1 study GETUG-12 Fizazi 2015	RCT	413	RR 0.75 (0.49, 1.15)	10 people per 100	7.5 people per 100 ((from 5 fewer to 12 more)	Not serious	Not serious	Not serious	Serious[2]	Moderate

1. 95% confidence intervals crosses the line of no effect – downgraded once
2. the 95% confidence interval for the effect size crossed one line of the MID – downgraded once

*Failure-free survival was defined as time from randomisation to first evidence of at least one of-: biochemical failure (defined as a rise of 50% above the within-24-week nadir and above 4ng/ml confirmed by rest or treatment), progression either locally, in lymph nodes, or in distant metastases or death from cancer
**Progression-free survival was defined as PSA progression (the first PSA increase to ≥0.4ng/ml, with a confirmatory PSA obtained within 2 weeks of the initially elevated value) , radiographic, or histological disease progression after systemic treatment or death from any cause, whichever came first as measured from the time of surgery. Progression free survival was measured from the date of disease progression.
***Relapse-free survival was defined as biochemical failure (an increase in serum PSA of more than 0.2ng/ml above the nadir, confirmed by another sample), onset of metastases on imaging, proven local relapse, use of salvage treatment and death.

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Hormone-sensitive metastatic prostate cancer

2 **Docetaxel (combined with ADT) versus Standard of Care (hormone therapy or ADT)**

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Overall survival – HR <1 favours docetaxel group										
3 studies GETUG-AFU15 Gravis 2013, CHAARTED Sweeney 2015, STAMPEDE James 2016	RCTs	2617	HR 0.77 (0.68, 0.86)	-	-	Not serious	Not Serious	Not serious	Not serious	High
Subgroup Analysis - • **Overall survival by dose 75mg/m2 of Docetaxel delivered every 3 weeks for 6 cycles– HR <1 favours docetaxel group**										
2 Studies STAMPEDE James 2016, CHAARTED Sweeney 2015	RCTs	2233	HR 0.74 (0.64, 0.84)	-	-	Not serious	Not serious	Not serious	Not serious	High
• **Overall survival by dose 75mg/m2 of Docetaxel delivered every 3 weeks for 9 cycles – HR <1 favours docetaxel group**										
1 Study GETUG-AFU15 Gravis 2013	RCT	385	HR 0.88 (0.68, 1.14)	-	-	Not serious	N/A	Not serious	Serious[1]	Moderate
• **Overall survival – high volume disease - HR <1 favours docetaxel group**										
2 Studies	RCTs	183	HR 0.67 (0.54, 0.83)	-	-	Not serious	Not serious	Not serious	Not serious	High

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
GETUG-AFU15 Gravis 2013, CHAARTED Sweeney 2015										
Overall survival – low volume disease - HR <1 favours docetaxel group										
2 Studies GETUG-AFU15 Gravis 2013, CHAARTED Sweeney 2015	RCTs	202	HR 0.87 (0.61, 1.23)	-	-	Not serious	Not serious	Not serious	Not serious	High
Clinical progression-free survival/ Failure-free survival/Relapse-free survival– HR <1 favours docetaxel group										
3 Studies GETUG-AFU15 Gravis 2013, STAMPEDE James 2016, CHAARTED Sweeney 2015,	RCTs	2617	HR 0.62 (0.57, 0.77)	-	-	Not serious	Not serious	Not serious	Not serious	High
Biochemical progression free survival – HR <1 favours docetaxel group										
1 Study GETUG-AFU15 Gravis 2013	RCT	385	HR 0.67 (0.54, 0.83)	-	-	Not Serious	N/A	Not serious	Not serious	High
Prostate cancer specific survival – HR <1 favours docetaxel group										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 study STAMPEDE James 2016	RCT	1442	HR 0.81 (0.66, 0.98)	-	-	Not serious	N/A	Not serious	Not serious	High
Quality of life scores during treatment phase (@ 6months) – EORTC – MD >1 favours docetaxel group										
1 Study GETUG-AFU15 Gravis 2013	RCT	385	MD -9.08 (-12.79, -5.37)	-	-	Serious[2]	N/A	Not serious	Not serious	Moderate

1. 95% confidence intervals crosses the line of no effect – downgraded once
2. Moderate risk of bias – due to self-completed questionnaires , downgraded once

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Appendix H – Excluded studies

Clinical studies

Short Title	Title	Reason for exclusion
Abdel-Rahman (2016)	Combined Chemohormonal Strategy in Hormone-Sensitive Prostate Cancer: A Pooled Analysis of Randomized Studies	Systematic review - no new studies identified for inclusion
Antonarakis (2012)	An immunohistochemical signature comprising PTEN, MYC, and Ki67 predicts progression in prostate cancer patients receiving adjuvant docetaxel after prostatectomy	Study does not contain any of the outcomes of interest
Aragon-Ching (2009)	VEGF inhibitors and prostate cancer therapy	Review article but not a systematic review
Aragon-Ching (2016)	Use of early chemotherapy for hormone-sensitive prostate cancer: time for CHAARTED	Review article but not a systematic review
Arlen (2006)	A randomized phase II study of concurrent docetaxel plus vaccine versus vaccine alone in metastatic androgen-independent prostate cancer	Population with hormone-refractory prostate cancer
Armstrong (2016)	A phase 2 multimodality trial of docetaxel/prednisone with sunitinib followed by salvage radiation therapy in men with PSA recurrent prostate cancer after radical prostatectomy	Phase 1 or 2 study single arm study
Beer (2004)	Quality of life and pain relief during treatment with calcitriol and docetaxel in symptomatic metastatic androgen-independent prostate carcinoma	Population with hormone-refractory prostate cancer
Beer (2015)	Autologous dendritic cell immunotherapy (DCVAC/PCa) added to docetaxel chemotherapy in a Phase III trial (viable) in men with advanced (mCRPC) prostate cancer	Population with hormone-refractory prostate cancer
Beltran (2017)	Impact of therapy on genomics and transcriptomics in high-risk prostate cancer treated with neoadjuvant docetaxel and androgen deprivation therapy	Study does not contain any of the outcomes of interest
Benedict (2010)	Hormone refractory carcinoma prostate with peritoneal metastases and malignant ascites without skeletal involvement: A case report and review of literature	Population with hormone-refractory prostate cancer
Berry (2006)	Quality of life and pain in advanced stage prostate cancer: results of a Southwest Oncology Group randomized trial comparing docetaxel and estramustine to mitoxantrone and prednisone	Population with hormone-refractory prostate cancer
Bilgin (2017)	Docetaxel or abiraterone in addition to androgen deprivation therapy in	Population with hormone-refractory

Short Title	Title	Reason for exclusion
	metastatic castration-sensitive prostate cancer	prostate cancer
Blanchard (2016)	Outcome According to Elective Pelvic Radiation Therapy in Patients With High-Risk Localized Prostate Cancer: A Secondary Analysis of the GETUG 12 Phase 3 Randomized Trial	Secondary publication of an included study that does not provide any additional relevant information
Botrel (2016)	Efficacy and Safety of Combined Androgen Deprivation Therapy (ADT) and Docetaxel Compared with ADT Alone for Metastatic Hormone-Naive Prostate Cancer: A Systematic Review and Meta-Analysis	Systematic review - no new studies identified for inclusion
Caffo (2015)	Clinical outcomes in a contemporary series of "young" patients with castration-resistant prostate cancer who were 60 years and younger	Population with hormone-refractory prostate cancer
Carles (2015)	A phase IIb trial of docetaxel concurrent with radiotherapy plus hormotherapy versus radio hormonotherapy in high-risk localized prostate cancer (QRT SOGUG trial): Preliminary report for design, tolerance, and toxicity	Conference abstract
Chen (2012)	Phase I study of concurrent weekly docetaxel, high-dose intensity-modulated radiation therapy (IMRT) and androgen-deprivation therapy (ADT) for high-risk prostate cancer	Phase 1 or 2 study single arm study
Chi (2008)	Multicenter Phase II Study of Combined Neoadjuvant Docetaxel and Hormone Therapy Before Radical Prostatectomy for Patients With High Risk Localized Prostate Cancer	Phase 1 or 2 study single arm study
Clarke (2013)	Survival with newly diagnosed metastatic prostate cancer in the "docetaxel era": Data from >600 patients in the control arm of the STAMPEDE trial (NCT00268476)	Conference abstract
De Paredes (2017)	Docetaxel in hormone-sensitive advanced prostate cancer; GENESIS-SEFH evaluation report	Study not reported in English
Dibiase (2011)	Long-term results of a prospective, phase II study of long-term androgen ablation, pelvic radiotherapy, brachytherapy boost, and adjuvant docetaxel in patients with high-risk prostate cancer	Phase 1 or 2 study single arm study
Domingo-Domenech (2008)	Serum HER2 extracellular domain predicts an aggressive clinical outcome and biological PSA response in hormone-independent prostate cancer patients treated with docetaxel	Not accessible
Dreicer (2004)	Phase II trial of neoadjuvant docetaxel before radical prostatectomy for locally advanced prostate cancer	Phase 1 or 2 study single arm study

Short Title	Title	Reason for exclusion
Eastham (2003)	Cancer and Leukemia Group B (CALGB) 90203: a randomized phase 3 study of radical prostatectomy alone versus estramustine and docetaxel before radical prostatectomy for patients with high-risk localized disease	Rationale paper
Farsaci (2016)	Analyses of pretherapy peripheral immunoscore and response to vaccine therapy	Does not contain a population of people with XXX
Febbo (2005)	Neoadjuvant docetaxel before radical prostatectomy in patients with high-risk localized prostate cancer	Conference abstract
Fizazi (2011)	Docetaxel-estramustine in high-risk localized prostate cancer: First results of the French Genitourinary Tumor Group phase III trial (GETUG 12)	Conference abstract
Fizazi (2012)	A phase III trial of docetaxel-estramustine in high-risk localised prostate cancer: a planned analysis of response, toxicity and quality of life in the GETUG 12 trial	Randomised controlled trial
Fizazi (2014)	Docetaxel-estramustine in localized high-risk prostate cancer: Results of the French Genitourinary Tumor Group GETUG 12 phase III trial	Conference abstract
Fizazi (2015)	Should docetaxel be standard of care for patients with metastatic hormone-sensitive prostate cancer? Pro and contra	Review article but not a systematic review
Francini (2011)	Bevacizumab and weekly docetaxel in patients with metastatic castrate-resistant prostate cancer previously exposed to docetaxel	Population with hormone-refractory prostate cancer
Francini (2017)	Prostate cancer: Developing novel approaches to castration-sensitive disease	Review article but not a systematic review
Friedman (2005)	Neoadjuvant docetaxel and capecitabine in patients with high risk/locally advanced prostate cancer: Preliminary results of a phase II study	Conference abstract
Garcia (2017)	Docetaxel in hormone-sensitive advanced prostate cancer; GENESIS-SEFH evaluation reporta	Study not reported in English
Garzotto (2010)	Phase 1/2 study of preoperative docetaxel and mitoxantrone for high-risk prostate cancer	Phase 1 or 2 study single arm study
Gravis (2013)	Identification of prognostic groups in patients with hormone-sensitive metastatic prostate cancer at the present time: An analysis of the GETUG 15 phase III trial	Conference abstract
Gravis (2014)	Patients' self-assessment versus investigators' evaluation in a phase III trial	Secondary publication of an included

Short Title	Title	Reason for exclusion
	in non-castrate metastatic prostate cancer (GETUG-AFU 15)	study that does not provide any additional relevant information
Gravis (2015)	Prognostic Factors for Survival in Noncastrate Metastatic Prostate Cancer: validation of the Glass Model and Development of a Novel Simplified Prognostic Model	Secondary publication of an included study that does not provide any additional relevant information
Guttilla (2014)	Multimodal treatment for high-risk prostate cancer with high-dose intensity-modulated radiation therapy preceded or not by radical prostatectomy, concurrent intensified-dose docetaxel and long-term androgen deprivation therapy: Eesults of a prospective phase II trial	Phase 1 or 2 study single arm study
Hahn (2017)	Novel androgen axis systemic therapies for metastatic hormone-sensitive prostate cancer	Review article but not a systematic review
Hainsworth (2006)	Weekly docetaxel/estramustine phosphate in patients with increasing serum prostate-specific antigen levels after primary treatment for prostate cancer: A phase II trial of the Minnie Pearl Cancer Research Network	Phase 1 or 2 study single arm study
Hamilton (2014)	Effect of concomitant medication use on outcomes of treatment and placebo arms of the COU-AA-301 and COU-AA-302 studies of abiraterone acetate (AA) in metastatic castration-resistant prostate cancer (mCRPC)	Conference abstract Population with hormone-refractory prostate cancer
Harshman (2017)	Lower PSA at 7 months is prognostic for improved overall survival (OS) in metastatic hormone sensitive prostate cancer (mHSPC) treated with ADT with and without docetaxel (D)	Conference abstract
Hassani (2017)	An update on clinical outcome data for a phase II randomized study comparing androgen deprivation therapy plus docetaxel versus androgen deprivation therapy alone in men with locally advanced/metastatic hormone sensitive prostate cancer	Conference abstract
Hatano (2011)	Retrospective analysis of an oral combination of dexamethasone, uracil plus tegafur and cyclophosphamide for hormone-refractory prostate cancer	Population with hormone-refractory prostate cancer
Heidenreich (2013)	A randomized, double-blind, multicenter, phase 2 study of a human monoclonal antibody to human alpha integrins (intetumumab) in combination with docetaxel and prednisone for the first-line treatment of patients with metastatic castration-resistant prostate cancer	Population with hormone-refractory prostate cancer

Short Title	Title	Reason for exclusion
Hussain (2001)	Docetaxel followed by hormone therapy after failure of definitive treatments for clinically localized/locally advanced prostate cancer: Preliminary results	Single arm
Hussain (2005)	Docetaxel followed by hormone therapy in men experiencing increasing prostate-specific antigen after primary local treatments for prostate cancer	Not a randomised study
Jackson (2016)	A phase 2 trial of salvage radiation and concurrent weekly docetaxel after a rising prostate-specific antigen level after radical prostatectomy	Phase 1 or 2 study single arm study
James (2009)	Systemic therapy for advancing or metastatic prostate cancer (STAMPEDE): a multi-arm, multistage randomized controlled trial	Rationale paper
James (2013)	Survival with newly-diagnosed metastatic prostate cancer in the "docetaxel era": Data from around 700 patients in the control arm of the STAMPEDE trial (NCT00268476)	Conference abstract
James (2015)	Docetaxel and/or zoledronic acid for hormone-naive prostate cancer: First overall survival results from STAMPEDE (NCT00268476)	Conference abstract
James (2015)	Survival with Newly Diagnosed Metastatic Prostate Cancer in the "Docetaxel Era": data from 917 Patients in the Control Arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019)	Secondary publication of an included study that does not provide any additional relevant information
James (2015)	Docetaxel (Doc) +/- zoledronic acid (ZA) for hormone-naive prostate cancer: First overall survival results from STAMPEDE & treatment effects within subgroups (NCT00268476)	Conference abstract
Kibel (2007)	Adjuvant weekly docetaxel for patients with high risk prostate cancer after radical prostatectomy: a multi-institutional pilot study	Duplicate reference
King (2012)	Insulin-like growth factor: Current concepts and new developments in cancer therapy	Review article but not a systematic review
Komura (2016)	Resistance to docetaxel in prostate cancer is associated with androgen receptor activation and loss of KDM5D expression	Review article but not a systematic review
Kumar (2004)	Phase I trial of weekly docetaxel with concurrent three-dimensional conformal radiation therapy in the treatment of unfavorable localized adenocarcinoma of the prostate	Phase 1 or 2 study single arm study
Kyriakopoulos (2016)	Chemohormonal therapy for hormone-sensitive prostate cancer	Review article but not a systematic review

Short Title	Title	Reason for exclusion
		Expert summary or commentary
Lavaud (2016)	How should we treat castration-resistant prostate cancer patients who have received androgen deprivation therapy (ADT) plus docetaxel upfront for hormone-sensitive diseae? Mature analysis of the GETUG-AFU 15 phase III trial	Conference abstract
Lei (2016)	Androgen-deprivation therapy alone versus combined with radiation therapy or chemotherapy for nonlocalized prostate cancer: A systematic review and meta-analysis	Study does not contain any relevant interventions
Li (2014)	Low dose of interferon-alpha improves the clinical outcomes of docetaxel in patients with castration-resistant prostate cancer: A pilot study	Population with hormone-refractory prostate cancer
Lin (2007)	Adjuvant weekly docetaxel for patients with high risk prostate cancer after radical prostatectomy: A multi-institutional pilot study. Kibel AS, Rosenbaum E, Kattan MW, Picus J, Dreicer R, Klein EA, Chatta GS, Nelson JB, DiPaola RS, Roth BJ, Cookson MS, Wilding G, Jarrard DF, Beer TM, Ryan CW, Petrylak DP, Benson MC, Partin AW, Garrett-Mayer E, Eisenberger MA, Siteman Cancer Center	Conference abstract
Liu (2010)	Rapamycin enhances the susceptibility of both androgen-dependent and -independent prostate carcinoma cells to docetaxel	Comparator in study does not match that specified in protocol
Marin-Aguilera (2014)	Epithelial-to-mesenchymal transition mediates docetaxel resistance and high risk of relapse in prostate cancer	Study does not contain any relevant interventions
Marino (2017)	Q-TWiST analysis of patients with metastatic castrate naive prostate cancer treated by androgen deprivation therapy with or without docetaxel in the randomised phase III GETUG-AFU 15 trial	Secondary publication of an included study that does not provide any additional relevant information
Marshall (2014)	Phase I trial of weekly docetaxel, total androgen blockade, and image-guided intensity-modulated radiotherapy for localized high-risk prostate adenocarcinoma	Phase 1 or 2 study single arm study
Martinet (2011)	Interpreting clinical assays for histone deacetylase inhibitors	Review article but not a systematic review
Mathew (2011)	Placental growth factor and soluble c-kit receptor dynamics characterize the cytokine signature of imatinib in prostate cancer and bone metastases	Population with hormone-refractory prostate cancer

Short Title	Title	Reason for exclusion
Mellado (2009)	Phase II trial of short-term neoadjuvant docetaxel and complete androgen blockade in high-risk prostate cancer	Not a randomised study
Miller (2016)	Chemotherapy for metastatic castrate-sensitive prostate cancer	Population with hormone-refractory prostate cancer
Montero (2005)	Docetaxel for treatment of solid tumours: A systematic review of clinical data	Population with hormone-refractory prostate cancer
Montgomery (2008)	Veterans Affairs Cooperative Studies Program Study 553: Chemotherapy After Prostatectomy, a Phase III Randomized Study of Prostatectomy Versus Prostatectomy with Adjuvant Docetaxel for Patients with High-Risk, Localized Prostate Cancer	Review article but not a systematic review
Morabito (2009)	Vandetanib (ZD6474), a dual inhibitor of vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) tyrosine kinases: Current status and future directions	Study does not contain any relevant interventions
Morris (2014)	A randomized, open label, multicenter, phase 3, 2-arm study of androgen deprivation with leuprolide (L), +/- docetaxel (D) for clinically asymptomatic prostate cancer (PC) subjects with a rising PSA following definitive local therapy: Safety results	Conference abstract
Morris (2015)	Efficacy analysis of a phase III study of androgen deprivation therapy (ADT) +/- docetaxel (D) for men with biochemical relapse (BCR) after prostatectomy	Conference abstract
Nilsson (2014)	1.5-year post-treatment follow-up of radium-223 dichloride (Ra-223) in patients with castration-resistant prostate cancer (CRPC) and bone metastases from the phase 3 ALSYMPCA study	Conference abstract
Nosov (2016)	Neoadjuvant Chemotherapy Using Reduced-Dose Docetaxel Followed by Radical Prostatectomy for Patients With Intermediate and High-Risk Prostate Cancer: A Single-Center Study	Not a randomised study
O'Brien (2010)	Histologic changes associated with neoadjuvant chemotherapy are predictive of nodal metastases in patients with high-risk prostate cancer	Not a randomised study Observational study
Oh (1999)	Docetaxel (Taxotere)-based chemotherapy for hormone-refractory and locally advanced prostate cancer	Review article but not a systematic review
Oh (2001)	Neoadjuvant docetaxel followed by radical prostatectomy in patients with high-risk	Population with hormone-refractory

Short Title	Title	Reason for exclusion
	localized prostate cancer: A preliminary report	prostate cancer
Oh (2005)	High-risk localized prostate cancer: integrating chemotherapy	Not accessible
Orphanos (2010)	Leptomeningeal metastases from prostate cancer: An emerging clinical conundrum	Review article but not a systematic review
Parekh (2015)	Insulin like growth factor and its association with lung, breast, and prostate cancer: A brief review	Review article but not a systematic review
Patel (2005)	Radiation Therapy Oncology Group 0521: a phase III randomized trial of androgen suppression and radiation therapy versus androgen suppression and radiation therapy followed by chemotherapy with docetaxel/prednisone for localized, high-risk prostate cancer	Rationale paper
Pedley (2011)	Tolerability and efficacy of anti-androgen manipulation versus taxotere and anti-androgen manipulation in patients with hormone-naive, high-risk/metastatic prostate cancer: A phase II, open-labeled, randomized study	Conference abstract
Petrylak (2004)	Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer	Population with hormone-refractory prostate cancer
Rajan (2015)	Feasibility study of a randomized controlled trial comparing docetaxel chemotherapy and androgen deprivation therapy with sequential prostatic biopsies from patients with advanced non-castration-resistant prostate cancer	Mixed population - locally and metastatic prostate cancer
Ramos-Esquivel (2016)	Androgen-deprivation therapy plus chemotherapy in metastatic hormone-sensitive prostate cancer. A systematic review and meta-analysis of randomized clinical trials	Systematic review - no new studies identified for inclusion
Rathkopf (2014)	Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302)	Population with hormone-refractory prostate cancer
Rulach (2017)	Real-world uptake, safety profile and outcomes of docetaxel in newly diagnosed metastatic prostate cancer	Not a randomised study Observational study
Santoni (2015)	Risk of pruritus in cancer patients treated with biological therapies: A systematic review and meta-analysis of clinical trials	Systematic review - no new studies identified for inclusion

Short Title	Title	Reason for exclusion
Scher (2012)	Effect of MDV3100, an androgen receptor signaling inhibitor (ARSI), on overall survival in patients with prostate cancer postdocetaxel: Results from the phase III AFFIRM study	Conference abstract
Sella (2008)	Neoadjuvant chemohormonal therapy in poor-prognosis localized prostate cancer	Single arm
Sharma (2017)	A game changing LATITUDE: Role of abiraterone plus prednisolone in metastatic hormone-sensitive prostate cancer	Expert summary or commentary
Stuyckens (2014)	Population pharmacokinetic analysis of abiraterone in chemotherapy-naïve and docetaxel-treated patients with metastatic castration-resistant prostate cancer	Population with hormone-refractory prostate cancer
Sweeney (2006)	ECOG 3805: CHAARTED - ChemoHormonal therapy versus androgen ablation randomized trial for extensive disease in prostate cancer	Not accessible
Sweeney (2014)	Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPrCa): An ECOG-led phase III randomized trial	Conference abstract
Sydes (2011)	Reflections on attempted Anglo-Japanese collaboration on STAMPEDE: A randomized controlled trial for men with prostate cancer	Review article but not a systematic review
Taplin (2001)	Docetaxel, estramustine, and short-term androgen withdrawal for patients with biochemical failure after definitive local therapy for prostate cancer	Not a randomised study
Taplin (2006)	Docetaxel, estramustine, and 15-month androgen deprivation for men with prostate-specific antigen progression after definitive local therapy for prostate cancer	Population with hormone-refractory prostate cancer
Thalgott (2014)	Long-term results of a phase II study with neoadjuvant docetaxel chemotherapy and complete androgen blockade in locally advanced and high-risk prostate cancer	Phase 1 or 2 study single arm study
Tombal (2014)	Enzalutamide monotherapy in hormone-naive prostate cancer: Primary analysis of an open-label, single-arm, phase 2 study	Phase 1 or 2 study single arm study
Trump (2003)	Chemotherapy of prostate cancer: present and future	Review article but not a systematic review
Tucci (2016)	Addition of docetaxel to androgen deprivation therapy for patients with hormone-sensitive metastatic prostate cancer: A systematic review and meta-analysis	Systematic review - no new studies identified for inclusion

Short Title	Title	Reason for exclusion
Uemura (2013)	Combination therapy of peptide vaccines and dexamethasone for chemotherapy naive castration resistant prostate cancer-a randomized phase-2 study	Conference abstract
Van Poppel (2005)	Recent docetaxel studies establish a new standard of care in hormone refractory prostate cancer	Review article but not a systematic review
van Soest (2015)	Irrefutable evidence for the use of docetaxel in newly diagnosed metastatic prostate cancer: Results from the STAMPEDE and CHAARTED trials	Review article but not a systematic review
Vicier (2016)	Modelling relapse in patients with high-risk localised prostate cancer treated randomly in the GETUG 12 phase III trial reveals two populations of relapsing patients	Conference abstract
Voskoboynik (2014)	'Charting a new course for prostate cancer' - Currying favor for docetaxel in hormone-sensitive metastatic prostate cancer	Not accessible
Vuky (2009)	Phase II trial of neoadjuvant docetaxel and gefitinib followed by radical prostatectomy in patients with high-risk, locally advanced prostate cancer	Phase 1 or 2 study single arm study
Vuky (2013)	Phase II trial of neoadjuvant docetaxel and CG1940/CG8711 followed by radical prostatectomy in patients with high-risk clinically localized prostate cancer	Phase 1 or 2 study single arm study
Wallis (2017)	Comparison of Abiraterone Acetate and Docetaxel with Androgen Deprivation Therapy in High-risk and Metastatic Hormone-naive Prostate Cancer: A Systematic Review and Network Meta-analysis	Systematic review - no new studies identified for inclusion
Walsh (2005)	Docetaxel and Estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer	Population with hormone-refractory prostate cancer
Wilke (2013)	The ELDORADO study: A phase II randomised study of concurrent weekly docetaxel, IMRT, and ltadt in patients with high-risk prostate cancer	Conference abstract
Witta (2004)	A phase I and pharmacokinetic study of exisulind and docetaxel in patients with advanced solid tumors	Not accessible

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Economic studies

Short Title	Title	Reason for exclusion
Collins et al. 2007	A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination	Not relevant population

Short Title	Title	Reason for exclusion
	with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer	
Grabner et al. 2011	Racial Variation in the Cost-Effectiveness of Chemotherapy for Prostate Cancer	Not cost-utility analysis
Guirgis et al. 2015	The value of anticancer drugs in metastatic castrate-resistant prostate cancer: economic tools for the community oncologist	Not relevant population
Norum et al. 2017	Treatments for Metastatic Prostate Cancer (mPC): A Review of Costing Evidence	Not cost-utility analysis
Pollard et al. 2017	Cost-effectiveness analysis of treatments for metastatic castration resistant prostate cancer	Not relevant population
Sanyal et al. 2016	Management of Localized and Advanced Prostate Cancer in Canada: A Lifetime Cost and Quality-Adjusted Life-Year Analysis	Docetaxel not explicitly considered as intervention
Zhang et al. 2017	Addition of docetaxel and/or zoledronic acid to standard of care for hormone-naïve prostate cancer: a cost-effectiveness analysis	Not applicable, selectively excluded given the presence of directly applicable evidence

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Appendix I – References

Clinical studies – Included

Fizazi K, Faivre L, Lesaunier F, et al. (2015) Androgen deprivation therapy plus docetaxel and estramustine versus androgen deprivation therapy alone for high-risk localised prostate cancer (GETUG 12): a phase 3 randomised controlled trial. The Lancet. Oncology 16(7), 787-94

Gravis G, Fizazi K, Joly F et al. (2013) Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. The lancet. Oncology 14(2), 149-158

Gravis G, Boher J M, Joly F et al. (2016) Androgen Deprivation Therapy (ADT) Plus Docetaxel Versus ADT Alone in Metastatic Non castrate Prostate Cancer: Impact of Metastatic Burden and Long-term Survival Analysis of the Randomized Phase 3 GETUG-AFU15 Trial. European Urology 70(2), 256-262

James ND, Sydes MR, Clarke NW et al. (2016) Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet (London, and England) 387(10024), 1163-1177

Schweizer Mt, Huang P, Kattan Mw et al. (2013) Adjuvant leuprolide with or without docetaxel in patients with high-risk prostate cancer after radical prostatectomy (TAX-3501): important lessons for future trials. Cancer 119(20), 3610-8

Christopher J Sweeney, M.B, B S, Yu-Hui Chen M.S, M P H, Michael Carducci M.D et al. (2015) Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 373(8), 737-746

Vale C L, Burdett S, Rydzewska L H. M et al. (2016) Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: A systematic review and meta-analyses of aggregate data. The Lancet Oncology 17(2), 243-256

Economic studies – Included

Woods BS, Sideris E, Sydes MR, Gannon MR, Parmar MK, Alzouebi M, Attard G, Birtle AJ, Brock S, Cathomas R, Chakraborti PR. Addition of Docetaxel to First-line Long-term Hormone Therapy in Prostate Cancer (STAMPEDE): Modelling to Estimate Long-term Survival, Quality-adjusted Survival, and Cost-effectiveness. European Urology Oncology. 2018 Sep 14.

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Appendix J – Research recommendations

Question	What is the prognostic value of different risk stratification methods for people with locally advanced prostate cancer?
Population	People with locally advanced prostate cancer
Intervention	Prognostic or predictive tools or prognostic factors
Comparator	Each other
Outcomes	Overall survival Progression free survival Tool/factor predictive accuracy (Model fit, Sensitivity, Specificity, Negative and Positive likelihood ratios)
Study design	Prospective or retrospective cohort studies investigating the prognosis of locally advanced prostate cancer with baseline measurement and at least 6 months follow up.
Potential criterion	**Explanation**
Importance to patients, service users or the population	The committee explained that currently there is no universal definition of 'locally advanced prostate cancer'. A risk stratification study will help to develop useful tools for identifying clinically meaningful levels of risks, which will in turn enable clinicians to tailor treatment accordingly
Relevance to NICE guidance	X Priority: Current NICE guidance is based on consensus. Research in this area will provide stronger evidence based on literature.
Current evidence base	Limited evidence, mostly based on consensus
Equality	No additional equality issues are envisaged relating to this study over and above those applying generally to vulnerable groups of people.
Feasibility	There is a large enough population of people with locally advanced prostate cancer, carrying out a trial in this area should be feasible

Appendix K – Economic evidence profiles

2

Study, population, country and quality	Data sources	Other comments	Incremental			Authors' conclusions	Uncertainty
			Cost (£)	Effect (QALYs)	ICER (£/QALY)		
Wood et al. (2018) Newly diagnosed metastatic and non-metastatic prostate cancer population starting long-term hormone therapy	Effects: time to first event and subsequent transitions modelled from STAMPEDE IPD Costs: within-RCT NHS resource-use (missing values multiply imputed); unit costs from NHS Ref-Costs. Drug prices from eMIT (BNF in sensitivity analysis). Additional neutropenia costs for docetaxel Utilities: within-RCT measurement of EQ-5D associated with states (additional docetaxel dis-benefit assumed to last for 1 year)	• Patient-level simulation (40 sims for each of the 2,962 patients in STAMPEDE = 118,480 sims per arm) • Docetaxel (75mg/m^2) in 6 x 3-wkly cycles + prednisolone 10mg daily. • Factorial trial design: some pts in each arm received zoledronic acid • Funded by UK MRC, CRUK, pharma including Sanofi-Aventis	Metastatic population			• The cost-effectiveness ratios for bisphosphonates are higher than commonly cited thresholds for conferring cost-effectiveness.	• Probabilistic results (methods not reported): • >99% prob docetaxel is cost-effective in both non-metastatic and metastatic patients • OSA: Results robust to all parameter variations (ICERs remain <£20K/QALY)
			£2,787	0.51	£5,514		
			Non-metastatic population				
			-£251	0.39	Dominant		

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