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[Intervention Review]

Taxane-based chemohormonal therapy for metastatic hormone-sensitive prostate cancer

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ABSTRACT

Background

There has been considerable development in the treatment of advanced prostate cancer over the last decade. A number of agents, including docetaxel, cabazitaxel, abiraterone acetate, enzalutamide and sipuleucel-T, have been reported to improve outcomes in men with castration-resistant disease and their use is being explored in hormone-sensitive prostate cancer.

Objectives

To assess the effects of early taxane-based chemohormonal therapy for newly diagnosed, metastatic, hormone-sensitive prostate cancer.

Search methods

We performed a comprehensive search using multiple databases (the Cochrane Library, MEDLINE, Embase, Scopus, Google Scholar, and Web of Science), trials registries, other sources of grey literature, and conference proceedings, up to 10 August 2018. We applied no restrictions on publication language or status.

Selection criteria

We included randomized or quasi-randomized controlled trials in which participants were administered taxane-based chemotherapy with systemic androgen deprivation therapy (ADT) within 120 days of beginning ADT versus ADT alone at the time of diagnosis of metastatic disease.

Data collection and analysis

Two review authors independently classified studies and abstracted data from the included studies. We performed statistical analyses using a random-effects model. We rated the quality of evidence according to the GRADE approach.

Main results

The search identified three studies in which 2,261 participants were randomized to receive either ADT alone, or taxane-based chemotherapy at a dose of 75mg per square meter of body surface area at three-weekly intervals for six or nine cycles in addition to ADT.

Primary outcomes

Taxane-based chemohormonal therapy for metastatic hormone-sensitive prostate cancer (Review)

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Early treatment with taxane-based chemotherapy in addition to ADT probably reduces death from any cause compared to ADT alone (hazard ratio (HR) 0.77, 95% confidence interval (CI) 0.68 to 0.87; moderate-certainty evidence); this would result in 94 fewer deaths per 1,000 men (95% CI 51 to 137 fewer deaths). We downgraded the certainty of evidence due to study limitations related to potential performance bias. Based on the results of one study with 375 participants, the addition of taxane-based chemotherapy to ADT may increase the incidence of Grade III to V adverse events compared to ADT alone (risk ratio (RR) 2.98, 95% CI 2.19 to 4.04; low-certainty evidence); this would result in 405 more Grade III to V adverse events per 1,000 men (95% CI 243 to 621 more events). We downgraded the certainty of evidence due to study limitations and imprecision.

Secondary outcomes

Early taxane-based chemotherapy in addition to ADT probably reduces the risk of prostate cancer-specific death (RR 0.79, 95% CI 0.70 to 0.89; moderate-certainty evidence). We downgraded the certainty of evidence due to study limitations related to potential performance and detection bias. The addition of taxane-based chemotherapy also probably reduces disease progression compared to ADT alone (HR 0.63, 95% CI 0.56 to 0.71; moderate-certainty evidence). We downgraded the certainty of evidence because of study limitations related to potential performance bias. The addition of taxane-based chemotherapy to ADT may result in a large increase in the risk of treatment discontinuation due to adverse events (RR 79.41, 95% CI 4.92 to 1282.78; low-certainty evidence). We downgraded the certainty of evidence due to study limitations and imprecision. This estimate is derived from a single study with no events in the control arm but a discontinuation rate of 20% in the intervention arm. Taxane-based chemotherapy may increase the incidence of adverse events of any grade (RR 1.11, 95% CI 1.06 to 1.17; low-certainty evidence). We downgraded our assessment of the certainty of evidence due to very serious study limitations. There may be a small improvement, which may not be clinically important, in quality of life at 12 months with combination treatment (mean difference (MD) 2.85 on the Functional Assessment of Cancer Therapy—Prostate scale, 95% CI 0.13 higher to 5.57 higher; low-certainty evidence). We downgraded the certainty of evidence for study limitations related to potential performance, detection and attrition bias.

Authors' conclusions

Compared to ADT alone, the early (within 120 days of beginning ADT) addition of taxane-based chemotherapy to ADT for hormone-sensitive prostate cancer probably prolongs both overall and disease-specific survival and delays disease progression. There may be an increase in toxicity with taxane-based chemotherapy in combination with ADT. There may also be a small, clinically unimportant improvement in quality of life at 12 months with taxane-based chemotherapy and ADT treatment.

PLAIN LANGUAGE SUMMARY

Adding taxane-based chemotherapy to androgen deprivation therapy for the treatment of metastatic hormone-sensitive prostate cancer

Review question

The aim of this review was to find out if adding taxane-based chemotherapy to hormone therapy improved outcomes in men with metastatic, hormone-sensitive prostate cancer. We collected and analysed all relevant studies to answer this question and found three studies.

Background

Of the men diagnosed with prostate cancer, approximately 16% will present with cancer that has spread at diagnosis. In addition, another 15% to 30% of men will get the disease again after having primary treatment. Hormone therapy (drugs to reduce the level of male hormones) has been the first treatment for advanced cancer but it does not cure it and eventually the cancer comes back. Recently studies have looked at whether chemotherapy (chemicals that kill cancer cells), when given early, improve how patients do.

Study characteristics

The evidence is current to August 2018. We found three studies (specifically, randomized controlled trials) with a total of 2,261 people. The studies compared docetaxel (an anti-cancer drug) and hormone therapy to hormone therapy alone.

Key results

Taxane-based chemotherapy in addition to hormone therapy likely improves overall and cancer-specific survival and reduces disease progression. There may also be a small but unimportant improvement in quality of life at 12 months. There may also be an increase in side effects when people are treated with taxane-based chemotherapy.

Certainty of evidence

We judged the certainty of the evidence to be moderate for time-to-death from any cause, risk of prostate cancer-specific death and the time to disease progression. This means that our estimates are likely to be close to the truth, but there were limitations in the studies that reduce our confidence in the results. The certainty of the evidence was low for Grade III to V adverse events (side effects), adverse events

of all grades, people stopping treatment due to adverse events, and quality of life. This means that the true effect of the treatment may be substantially different from what this review shows, because of limitations in the studies and imprecision (variability in estimates).

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Early taxane-based chemotherapy and androgen deprivation therapy (ADT) compared to ADT only for metastatic hormone-sensitive prostate cancer

Early taxane-based chemotherapy and ADT compared to ADT only for metastatic hormone-sensitive prostate cancer

Participants: men with metastatic hormone-sensitive prostate cancer

Setting: multicenter

Intervention: early docetaxel with androgen deprivation therapy

Control: androgen deprivation therapy only

Outcomes	Nº of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with ADT only	Risk difference with taxane-based chemotherapy and ADT
Time to death due to any cause (absolute effect size estimates based on all-cause mortality at 5 years) Follow-up: median 43 to 84 months	2,261 (3 RCTs)	⊕⊕⊕⊖ MODERATE ³	HR 0.77 (0.68 to 0.87)	Study population ¹	
				610 per 1,000	94 fewer per 1,000 (137 fewer to 51 fewer)
				General Population ²	
				702 per 1,000	96 fewer per 1,000 (141 fewer to 51 fewer)
Grade III to V adverse events Follow-up: median 50 months	375 (1 RCT)	⊕⊕⊖⊖ LOW ⁴	RR 2.98 (2.19 to 4.04)	Study population	
				204 per 1,000	405 more per 1,000 (243 more to 621 more)
Prostate cancer-specific death ⁵ Follow-up: median 29 to 84 months	2,261 (3 RCTs)	⊕⊕⊕⊖ MODERATE ⁶	RR 0.79 (0.70 to 0.89)	Study population ⁷	
				512 per 1,000	108 fewer per 1,000 (154 fewer to 56 fewer)
Time to progression (absolute effect size estimates based on progression rate at 5 years)	2,261 (3 RCTs)	⊕⊕⊕⊖ MODERATE ⁶	HR 0.63 (0.56 to 0.71)	Study population ⁸	
				822 per 1,000	159 fewer per 1,000

Follow-up: median 43 to 84 months				(202 fewer to 116 fewer)	
Discontinuation due to adverse events	385 (1 RCT)	⊕⊕⊕⊕ LOW ⁹	RR 79.41 (4.92 to 1282.78)	Study population	
Follow-up: median 50 months				0 per 1,000	41 more per 1,000 (25 more to 1000 more)
All adverse events	375 (1 RCT)	⊕⊕⊕⊕ LOW ⁴	RR 1.11 (1.06 to 1.17)	Study population	
Follow-up: median 50 months				898 per 1,000	99 more per 1,000 (54 more to 153 more)
Quality of life at 12 months (measured with the Functional Assessment of Cancer Therapy-Prostate (FACT-P) scale, higher score is better)	790 (1 RCT)	⊕⊕⊕⊕ LOW ¹⁰	-	The mean quality-of-life (FACT-P) score in the control arm was 116.4	MD 2.85 higher (0.13 higher to 5.57 higher)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **HR:** hazard ratio; **RR:** Risk ratio; **OR:** Odds ratio; **MD:** mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ Baseline risk of death for any cause was calculated from the 5-year event rate of control group from CHAARTED trial (Kyriakopoulos 2018).

² Population data from SEER registry, prostate cancer stage IV 5-year survival (70.2%) in the pre-docetaxel era (2007 to 2013).

³ Severe concerns regarding study limitations (high risk of performance bias) contributed to our decision to downgrade by one level overall.

⁴ Severe concerns regarding study limitations (high risk of performance and detection bias), imprecision (wide CI consistent with both large and very large increase in grade III to V adverse events), and additional concerns about selective reporting (outcome only adequately reported by one of three trials) contributed to our decision to downgrade by two levels overall.

⁵ We planned to assess this as a time-to-event outcome (time to prostate cancer-specific death), but we evaluated this as a dichotomous outcome due to insufficient data.

⁶ Severe concerns regarding study limitations (high risk of performance bias and unclear risk of detection bias) contributed to our decision to downgrade by one level overall.

⁷ Baseline risk of prostate cancer-specific death was calculated from the 5-year event rate of control group from the GETUG-AFU15 trial.

⁸ Baseline risk of progression was calculated from the 5-year event rate of control group from CHAARTED trial (Kyriakopoulos 2018).

⁹ Severe concerns regarding study limitations (high risk of performance and detection bias), imprecision (wide confidence intervals suggesting small and very large increase in treatment discontinuation due to adverse events), and additional concerns about selective reporting (outcome only adequately reported by one of three trials) contributed to our decision to downgrade by two levels overall.

¹⁰ Very severe concerns regarding study limitations (high risk of detection, performance and attrition bias) contributed to our decision to downgrade by two levels overall.

BACKGROUND

Description of the condition

Prostate cancer is the most frequently diagnosed cancer amongst men in high-income countries and causes over 300,000 deaths worldwide (Torre 2015). In the USA, prostate cancer accounts for one in five new diagnoses of all cancers and is the second leading cause of death from cancer amongst men (Siegel 2016). Most prostate cancers tend to be localized at the time of diagnosis and are managed with active monitoring/surveillance, radical surgery or radiation therapy (Hamdy 2016). However, a subgroup of men experience local or distant disease recurrence after local therapy. The estimated incidence of metastases following surgery or radiotherapy is 2.4 and 3.0 events per 1,000 person-years, respectively (Hamdy 2016). Approximately 16% of men present with regional or distant-stage disease at the time of initial diagnosis (Siegel 2016). Therefore, the burden of advanced prostate cancer is considerable.

Since Huggins and colleagues elucidated the androgen-dependent nature of prostate cancer, androgen deprivation therapy has underpinned the management of locally advanced and metastatic hormone-sensitive prostate cancer (Huggins 1941). Although androgen deprivation therapy demonstrates antitumor activity, with marked reduction of the prostate-specific antigen (PSA) in the majority of men, it is not curative. Most men eventually experience progression of their cancer despite ongoing hormone treatment, which is a lethal disease state referred to as castration-resistant prostate cancer. This progression occurs after a mean of 11 months on androgen deprivation therapy (James 2015). The mechanisms involved in the progression of disease are not entirely understood and currently thought to be a multifactorial process that facilitates androgen receptor activity through amplification, mutations, splice variants and aberrant activation (Tilki 2016). Once in this resistant state, men face a poor prognosis with a pooled median survival of 14 months (Kirby 2011). Additionally, castration-resistant disease is associated with considerable morbidity and a negative impact on quality of life. It has been reported that 45% of men were burdened by bone pain at the time of diagnosis with this lethal disease state (Inoue 2009). At a mean follow-up of 18 months, 80% of men experienced bone pain. Moreover, increased incidence of major skeletal events, such as vertebral collapse, fractures and spinal cord compression, is evident with disease progression (Berruti 2005).

Advanced prostate cancer treatment has undergone considerable transformation since the early 2000s, prior to which no treatment had been shown to confer a survival benefit. Early randomized trials that examined the role of chemohormonal therapy using chemotherapeutic agents such as epirubicin (Pummer 1997), estramustine (Janknegt 1997), cyclophosphamide (Murphy 1983), or a combination of ketoconazole plus doxorubicin alternating with vinblastine plus estramustine, demonstrated no improvement in survival (Millikan 2008). However, there was a landmark discovery in 2004 when two studies reported prolonged overall survival in men with metastatic castration-resistant cancer who were administered docetaxel (Petrylak 2004; Tannock 2004). The seminal findings with docetaxel led to re-consideration of the concept of early chemohormonal therapy utilizing newer agents to improve patient outcomes. The newer drugs have all focused on men with castration-resistant prostate cancer; however, this has changed with the introduction of docetaxel earlier in the disease stage concomitantly with the time of systemic androgen ablation.

Description of the intervention

Docetaxel is a second-generation taxane chemotherapeutic agent that is derived from 10-Deacetylbaicatin III obtained from European yew tree needles (*Taxus baccata*) (Engels 2005). It is currently approved for use in a range of advanced cancers including metastatic castration-resistant prostate cancer. In this latter setting, docetaxel is administered as an intravenous infusion of 75 mg per square meter of body surface, every 21 days. It has also been used every two weeks in a Phase II trial in metastatic castration-resistant prostate cancer patients (Kellokumpu-Lehtinen 2013). This is prescribed in combination with oral prednisolone 5 mg twice daily.

At standard doses, docetaxel has been reported to have linear pharmacokinetics with a mean half-life of 11 hours. In plasma, over 90% of the drug is bound to α 1-acid glycoprotein, albumin and lipoproteins. The concentration of α 1-acid glycoprotein has been demonstrated to have the most impact on both clearance and the amount of unbound, pharmacologically active substance. The drug is primarily metabolized through hepatic CYP3A pathways with metabolites eliminated in the faeces and urine (Loos 2003). Therefore, medications that induce CYP3A activity, such as antiepileptic drugs, decrease the efficacy of docetaxel. In contrast, drugs that inhibit hepatic enzymes decrease clearance.

Adverse effects of the intervention

Phase I trials have demonstrated that the dose-limiting toxicity of docetaxel was neutropenia (Taguchi 1994). Just under one-third (32%) of the group receiving docetaxel every three weeks in the TAX 327 study reported grade 3 or 4 neutropenia (Tannock 2004). Other severe complications experienced include anemia, thrombocytopenia and fatigue. One in 10 men had impaired left ventricular function following treatment. Furthermore, over one-half of the group reported fatigue (53%) and alopecia (65%). There was no significant trend to decreased adverse events with weekly docetaxel therapy compared to dosing every three weeks. Meanwhile, Petrylak and colleagues found that men administered docetaxel plus estramustine displayed higher incidences of febrile neutropenia, cardiovascular events, nausea and vomiting, metabolic disturbances and neurologic events, compared to men who received mitoxantrone plus prednisone (Petrylak 2004). However, there was no significant difference of grade 3 or greater neutropenia between the groups. It is important to note the adverse event outcomes reported in these trials may not be truly representative of routine clinical practice. It was observed that men with metastatic castration-resistant prostate cancer who received docetaxel while enrolled in a clinical trial, including TAX 327 (Tannock 2004), were younger, had a better performance status and experienced less toxicity from their treatment than men managed out of a trial protocol (Templeton 2013).

How the intervention might work

Taxanes bind to tubulin on microtubules and result in increased polymerization, thus interfering with mitosis. Microtubules are protein polymers which are an integral component of the cytoskeleton and have several functions including cell signalling, translocation of cellular cargo and cell division. They are essential for nearly all steps of mitosis as they are involved in the attachment of chromosomes to the spindle, congression and synchronous separation during anaphase and telophase. It has been shown that even a single chromosome unable to attach to a spindle is sufficient

to induce cell cycle arrest, and the cell subsequently undergoes apoptosis (Jordan 1996).

Publications have proposed that taxanes also interact with the androgen receptor in neoplastic prostate cells (Darshan 2011; Gan 2009). Using tissue microarrays, it has been demonstrated that treatment with docetaxel results in significant decrease of ligand-induced androgen receptor nuclear translocation (Zhu 2010). This subsequently results in a reduction of androgen receptor transcriptional activity measured by PSA messenger ribonucleic acid (mRNA) expression. These two mechanisms of decreased androgen receptor activity and cell cycle arrest are hypothesized to slow the growth and progression of metastatic prostate cancer.

Delaying the development of castration-resistant prostate cancer has important implications. Men are able to maximize their quality of life by delaying the potential morbidity associated with complications arising from castration-resistant disease (Saad 2017), and the need for further treatment. Moreover, administration of chemotherapy during the early stages of metastatic prostate cancer, rather than after progression to a castration-resistant state, has its own benefits. The higher disease burden and subsequent overall decline in functional status that is experienced with the development of castration-resistant prostate cancer will exclude a sizable proportion of men from receiving chemotherapy at this late stage. Furthermore, the typically superior health status of men during the early stages of metastatic prostate cancer diagnosis enhances their capacity to withstand the toxicities of chemotherapy.

Why it is important to do this review

Early chemotherapy is beginning to be widely used to treat men with newly diagnosed metastatic prostate cancer, representing a paradigm shift in the management of these men. This is reflected in current clinical practice guidelines such as those of the National Comprehensive Cancer Network (Mohler 2017), European Society of Medical Oncology (Parker 2015), and European Association of Urology (Cornford 2017), with major implications for clinical care pathways and resource utilization. Guidelines differ in their recommendations as to whether all men with metastatic prostate cancer should receive early chemotherapy, or only men with higher volume disease.

Several systematic reviews exist that have sought to critically appraise the entire body of trial evidence addressing this question. Tucci and colleagues attempted to answer this question, but they did not assess the benefit of early chemotherapy on disease-specific survival or use the GRADE approach to evaluate the evidence (Tucci 2016). Similar shortcomings are evident in the other two systematic reviews on this topic (Botrel 2016; Vale 2016). Therefore, this Cochrane Review aims to use the most methodologically rigorous approach to critically evaluate the evidence in a prescribed manner and focus on outcomes that are important to men with metastatic hormone-sensitive prostate cancer.

OBJECTIVES

To assess the effects of early taxane-based chemohormonal therapy for newly diagnosed metastatic hormone-sensitive prostate cancer.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized or quasi-randomized controlled trials, regardless of their publication status or language of publication. We excluded cluster-randomized and cross-over randomized studies.

Types of participants

We included studies that enrolled men with a confirmed histological diagnosis of adenocarcinoma of the prostate and radiologic evidence of metastases as determined by cross-sectional imaging (computer tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) with or without bone scans. This included both men who had and had not undergone local therapy. Only men receiving taxane-based chemotherapy for their prostate cancer were included. Men were required to have commenced chemotherapy within 120 days of beginning androgen deprivation therapy to be considered as receiving early combination therapy. Men who had previously received adjuvant or neoadjuvant androgen deprivation therapy were permitted in the study if the development of metastases occurred at least 12 months following cessation of hormone therapy. Men receiving concurrent osteoprotective therapy (e.g. bisphosphonates) were also eligible.

We excluded men with advanced prostate cancer who received chemotherapy without known metastases, and those who received prior chemotherapy of any agent for their prostate cancer.

Types of interventions

We considered the following interventions. Concomitant interventions had to be the same in the experimental and comparator groups to establish fair comparisons.

Experimental interventions

- Taxane-based chemotherapy in combination with androgen deprivation therapy (using methods outlined under 'Comparator intervention' below).

Comparator interventions

- Androgen deprivation therapy only (using luteinizing hormone-releasing hormone agonist or antagonist; combination of antiandrogen plus luteinizing hormone-releasing hormone agonist (maximum androgen blockade); or bilateral orchiectomy).

Types of outcome measures

We did not use the measurement of the outcomes assessed in this review as an eligibility criterion.

Primary outcomes

- Time to death due to any cause.
- Grade III to V adverse events.

Secondary outcomes

- Time to death due to prostate cancer (analyzed as prostate cancer-specific death, see [Differences between protocol and review](#)).

- Time to progression.
- Discontinuation due to adverse events.
- All adverse events.
- Quality of life.

Method and timing of outcome measurement

- Time to death due to any cause: the time from randomization until death from any cause.
- Grade III to V adverse events: grade 3 to 5 adverse events according to the Common Toxicity Criteria (CTCAE) v3.0, occurring at any time during treatment; e.g. sudden death, neutropenia, febrile neutropenia, fatigue, gastrointestinal disorders (including diarrhea, constipation and vomiting), stomatitis, neuropathy, thromboembolism, thrombocytopenia or renal impairment.
- Time to death due to prostate cancer (analyzed as prostate cancer-specific death): the time from randomization until death from prostate cancer.
- Time to progression: the time from randomization until clinical, biochemical or radiographic progression.
- Discontinuation due to adverse events: the number of participants ceasing treatment due to an adverse event caused by the treatment.
- All adverse events: all grades of adverse events measured by CTCAE v3.0 (Trotti 2003).
- Quality of life: measured by validated instruments such as the 12-item Short Form (SF-12), 36-item Short Form (SF-36) or Functional Assessment of Cancer Therapy (FACT) questionnaire.

If we were unable to retrieve the necessary information to analyze time-to-event outcomes, we assessed the number of events per total for dichotomized outcomes at one, three and five years after commencing chemohormonal therapy.

Search methods for identification of studies

We performed a comprehensive search up to 10 August 2018, with no restrictions on the language of publication or publication status. We planned to rerun the searches within three months prior to the anticipated publication of the review, should the original search date have fallen outside of this timeframe.

Electronic searches

We searched the following sources on 10 August 2018, from the inception of each database, with no date restrictions.

- The Cochrane Library:
 - *Cochrane Database of Systematic Reviews* (CDSR);
 - Cochrane Central Register of Controlled Trials (CENTRAL);
 - Database of Abstracts of Reviews of Effects (DARE);
 - Health Technology Assessment Database (HTA).
- MEDLINE (PubMed).
- Embase (Ovid).

We also searched the following.

- ClinicalTrials.gov (www.clinicaltrials.gov/).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (apps.who.int/trialsearch/).

- Metaregister of controlled trials (www.controlled-trials.com/mrct/).
- EU clinical trials register (www.clinicaltrialsregister.eu/ctr-search/search).

If we detected additional relevant key words during any of the electronic or other searches, we planned to modify the electronic search strategies to incorporate these terms, and to document the changes.

Searching other resources

We tried to identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included trials, reviews, meta-analyses and health technology assessment reports. We also contacted study authors of included trials to identify any further studies that we may have missed. We planned to contact drug/device manufacturers for ongoing or unpublished trials.

We searched abstract proceedings of relevant meetings (American Urological Association, European Urological Association, American Society of Clinical Oncology, European Society of Medical Oncology) from 2013 to 2017 for unpublished studies.

Data collection and analysis

Selection of studies

We used reference management software (EndNote) to identify and remove potential duplicate records and then imported these references into *Covidence*, a web-based program for systematic review development. When more than one report of the same trial was available, we included the most up-to-date publication in the analysis. In the event that a study had more than one publication, we grouped publications so that each study, rather than each publication, was the unit of interest. Two review authors (NS, YP) independently scanned the abstract, title (or both) of the records retrieved, to determine which studies should be assessed further. Two review authors (NS, YP) investigated all potentially relevant records as full text, mapped records to studies, and classified studies as included studies, excluded studies, studies awaiting classification, or ongoing studies, in accordance with the criteria for each provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We planned to resolve any discrepancies through consensus or recourse to a third review author (PD). If resolution of a disagreement was not possible, we planned to designate the study as 'awaiting classification' and to contact study authors for clarification. We documented reasons for exclusion of studies that may have reasonably been expected to be included in the review in a 'Characteristics of excluded studies' table. We presented an adapted PRISMA flow diagram showing the process of study selection (Liberati 2009).

Data extraction and management

We developed a dedicated data abstraction form that we piloted ahead of time.

For studies that fulfilled the inclusion criteria, two review authors (NS, YP) independently abstracted the following information, which we report in the 'Characteristics of included studies' table.

- Study design.

- Study dates (if dates were not available then this was reported as such).
- Study settings and country.
- Participant inclusion and exclusion criteria (including participant comorbidities, disease stage, pretreatment).
- Participant details, baseline demographics (including participant age, disease stage).
- Number of participants by study and by study arm.
- Details of relevant experimental and comparator interventions (including dose, route, frequency and duration).
- Definitions of relevant outcomes, and method and timing of outcome measurement as well as any relevant subgroups.
- Study funding sources.
- Declarations of interest by primary investigators.

We extracted outcome data relevant to this Cochrane Review as needed for calculation of summary statistics and measures of variance. For dichotomous outcomes such as adverse events, we attempted to obtain numbers of events and totals for population of a 2 × 2 table, as well as summary statistics with corresponding measures of variance. For continuous outcomes such as quality-of-life scores, we attempted to obtain means and standard deviations or data necessary to calculate this information. For time-to-event outcomes, we extracted the hazard ratio (HR) from published data according to published guidance (Parmar 1998; Tierney 2007), with corresponding measures of variance or data necessary to calculate this information.

We planned to resolve any disagreements by discussion, or, if required, by consultation with a third review author (AL).

We provided information, including trial identifier, about potentially relevant ongoing studies in a 'Characteristics of ongoing studies' table.

We attempted to contact authors of included studies to obtain key missing data as needed.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents or multiple reports of a primary study, we maximized the yield of information by mapping all publications to unique studies and collating all available data. We used the most complete data-set aggregated across all known publications. In case of doubt, we gave priority to the publication reporting the longest follow-up associated with our primary or secondary outcomes.

Assessment of risk of bias in included studies

Two review authors (NS, YP) assessed the risk of bias of each included study independently. We planned to resolve disagreements by consensus, or by consultation with a third review author (PD).

We assessed risk of bias using Cochrane's 'Risk of bias' assessment tool (Higgins 2011b). We assessed the following domains.

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).

- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other sources of bias.

We judged risk of bias domains as 'low risk,' 'high risk' or 'unclear risk' and evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We have presented a 'Risk of bias' summary figure to illustrate these findings.

For performance bias, we judged all outcomes to be similarly susceptible and rated them in one group.

For detection bias (blinding of outcome assessment), we evaluated the risk of bias separately for each outcome, and we grouped outcomes according to whether they were measured subjectively or objectively when reporting our findings in the 'Risk of bias' tables.

We defined the following endpoints as 'subjective' outcomes.

- Time to progression.
- Time to death due to prostate cancer (analyzed as prostate cancer-specific death).
- Grade III to V adverse events.
- Any adverse events.
- Discontinuation due to adverse event.
- Quality of life.

We defined the following endpoint as an 'objective' outcome for which blinding of outcome assessors is not important.

- Time to death due to any cause.

We assessed attrition bias (incomplete outcome data) on an outcome-specific basis, and presented the judgment for each outcome separately when reporting our findings in the 'Risk of bias' tables. If appropriate, we created groups of outcomes with similar reporting characteristics (e.g. grade III to V events and any adverse events) to facilitate both the 'Risk of bias' ratings and presentation.

We further summarized the risk of bias across domains for each outcome in each included study, as well as across studies and domains for each outcome, in accordance with the approach for summary assessments of the risk of bias presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

Measures of treatment effect

We expressed dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs). We expressed continuous data as mean differences (MDs) with 95% CIs. We expressed time-to-event data as HRs with 95% CIs. We analysed the data using RevMan 5 software (RevMan 2014). In future updates of this review, should different studies use different measures to assess the same continuous outcome, we will express data as standardized mean differences with 95% CIs.

Unit of analysis issues

The unit of analysis was the individual participant. If in future updates of this review we identify trials with more than two intervention groups for inclusion, we will handle these in accordance with guidance provided in the *Cochrane Handbook for*

Systematic Reviews of Interventions (Higgins 2011c). We excluded cross-over trials and cluster-randomized trials.

Dealing with missing data

We attempted to obtain missing data from study authors and performed intention-to-treat (ITT) analyses if data were available; we otherwise performed available-case analyses. We investigated attrition rates (e.g. dropouts, losses to follow-up and withdrawals), and critically appraised issues of missing data. We did not impute missing data.

Assessment of heterogeneity

We identified heterogeneity (inconsistency) through visual inspection of the forest plots to assess the amount of overlap of CIs. We also used the I^2 statistic, which quantifies inconsistency across studies, to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003); we interpreted the I^2 statistic as follows (Deeks 2011):

- 0% to 40%: may not be important;
- 30% to 60%: may indicate moderate heterogeneity;
- 50% to 90%: may indicate substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

When we found heterogeneity, we attempted to determine possible reasons for it by examining individual study and subgroup characteristics.

Assessment of reporting biases

We attempted to obtain study protocols to assess for selective outcome reporting.

Data synthesis

We summarized the data using a random-effects model, and will do so in future updates of this review unless there is good evidence for homogeneous effects across studies. We interpreted random-effects meta-analyses with due consideration of the whole distribution of effects. In addition, we performed statistical analyses according to the statistical guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). For dichotomous outcomes, we used the Mantel-Haenszel method; for continuous outcomes, we used the inverse variance method; and for time-to-event outcomes, we used the generic inverse variance method. We used Review Manager 5 software to perform analyses (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

We expected the following characteristics to introduce clinical heterogeneity, and carried out subgroup analyses with investigation of interactions.

- Volume of metastases: high volume (defined according to expert consensus (Gillesen 2015) as visceral, four or more bone metastases including one beyond the pelvis and vertebral column, or both) versus low volume.
- Type of metastases: nodal metastases only versus visceral, bone, nodal metastases, or a combination of these.

We used the test for subgroup differences in Review Manager 5 to compare subgroup analyses if there was at least one study with

the data available for our pre-defined subgroups (RevMan 2014). Furthermore, unless the trial(s) were stratified for the subgroups we downgraded the quality of evidence.

Sensitivity analysis

We performed sensitivity analyses to explore the influence of the following factors (when applicable) on effect sizes.

- Restricting the analysis by taking into account risk of bias, by excluding studies at 'high risk' or 'unclear risk.'

'Summary of findings' table

We have presented a 'Summary of findings' table, reporting the following outcomes listed according to priority.

- Time to death due to any cause.
- Grade III to V adverse events.
- Time to death due to prostate cancer (analyzed as prostate cancer-specific death).
- Time to progression.
- Discontinuation due to adverse events.
- All adverse events.
- Quality of life.

We present the overall certainty of the evidence for each outcome according to the GRADE approach, which takes into account five criteria relating to internal validity (risk of bias, inconsistency, imprecision, publication bias), and external validity (such as directness of results) (Guyatt 2008). For each comparison, two review authors (NS, YP) independently rated the quality of evidence for each outcome as 'high', 'moderate', 'low' or 'very low' using GRADEpro GDT. We planned to resolve any discrepancies by consensus, or, if needed, by arbitration by a third review author (PD). For each comparison, we presented a summary of the evidence for the main outcomes in a 'Summary of findings' table, which provides key information about the best estimate of the magnitude of the effect in relative terms and absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of the overall confidence in effect estimates for each outcome (Guyatt 2011; Schünemann 2011).

For time-to-event outcomes, we generated absolute effect size estimates based on defined control event rates at defined timepoints. For the purpose of these estimates in the 'Summary of findings' table, time-to-event outcomes were relabeled, for example, to time to death from any cause to all-cause mortality.

RESULTS

Description of studies

Results of the search

We identified 346 records through electronic database searching. We found two additional records through handsearching abstract proceedings of relevant meetings (Sweeney 2016 and Patrick-Miller 2016a, both listed below as additional references to Sweeney 2015), and none in the grey literature repository. After removal of duplicates, we screened the titles and abstracts of 326 records of which we excluded 314. We screened 12 full-text articles and

excluded one that did not meet the inclusion criteria. We included a total of three studies (11 records) in this review. We did not identify any trials which are either ongoing, or completed but awaiting

assessment. The flow of literature through the assessment process is shown in the PRISMA flowchart ([Figure 1](#)).

Figure 1. Study flow diagram.

Included studies

Details of the included trials are presented elsewhere ([Characteristics of included studies](#); [Table 1](#); [Table 2](#)).

Source of data

All three included trials were identified through the literature search ([Gravis 2013](#); [James 2016](#); [Sweeney 2015](#)). The GETUG-AFU 15 trial had multiple publications, the most recent of which reported updated, long-term outcomes ([Gravis 2013](#)). A conference abstract of the CHAARTED trial was also included ([Sweeney 2015](#)). We contacted all the trial authors and received a reply from each, but we only obtained additional unpublished data from one study ([Gravis 2013](#)).

Study design and settings

All the included studies were parallel, randomized controlled trials ([Gravis 2013](#); [James 2016](#); [Sweeney 2015](#)). The trials were all open-label, multicenter and were likely conducted in the outpatient setting. The studies were performed in France ([Gravis 2013](#)), the UK ([James 2016](#)) and the USA ([Sweeney 2015](#)).

Participants

This review includes a total of 2,261 randomized participants with metastatic hormone-sensitive prostate cancer, of whom 951 received docetaxel in addition to androgen deprivation therapy (ADT). One trial also enrolled 1,145 participants with non-metastatic disease but we did not include this subgroup in the review ([James 2016](#)). The median age and prostate-specific antigen (PSA) level at randomization of participants ranged from 63 to 64 years old and 25.8 nanograms per milliliter (ng/mL) to 50.9 ng/mL, respectively ([Gravis 2013](#); [Sweeney 2015](#)). Separate demographic characteristics for participants with metastatic disease were not reported in [James 2016](#). The proportion of participants with high-volume metastases ranged from 48% to 65% ([Gravis 2013](#); [Sweeney 2015](#)); this information was not reported in [James 2016](#). The majority of participants had an initial Gleason score above seven in all trials. The proportion of participants with prior local treatment before the diagnosis of metastatic disease ranged from 4% to 28% ([Gravis 2013](#); [James 2016](#); [Sweeney 2015](#)).

Participants over the age of 18 years old were eligible for inclusion in the trials if they had a pathological diagnosis of prostate cancer and radiological evidence of metastatic disease ([Gravis 2013](#); [James 2016](#); [Sweeney 2015](#)). One trial also included individuals without a histological diagnosis as long as they had a clinical scenario that was consistent with prostate cancer ([Sweeney 2015](#)). Participants were also required to have an adequate functional status, defined as Eastern Cooperative Oncology Group (ECOG) score of zero to two in all trials, and be fit for chemotherapy. Prior neoadjuvant or adjuvant hormone therapy (or both) was allowed in the included studies if it was completed at least 12 months prior to randomization. The receipt of any previous chemotherapy in the adjuvant or neoadjuvant setting (or both) was an exclusion criterion in two trials ([James 2016](#); [Sweeney 2015](#)), but this was permitted in the third trial if the course of chemotherapy had been completed at least 12 months prior to randomization and there had not been any evidence of PSA or disease progression (or both) for at least one year ([Gravis 2013](#)).

Interventions and comparators

The included trials administered intravenous docetaxel at 75 mg per square meter of body-surface area every three weeks for either six ([James 2016](#); [Sweeney 2015](#)), or nine cycles ([Gravis 2013](#)), in addition to ADT. Daily prednisolone was administered during the docetaxel treatment phase in one trial ([James 2016](#)), but in the other trials this was either not mandated ([Sweeney 2015](#)), or reported ([Gravis 2013](#)). In one arm of the STAMPEDE trial, zoledronic acid was also administered at 4 mg for six three-weekly cycles, and then every four weeks for two years in combination with the aforementioned docetaxel regimen and ADT ([James 2016](#)).

The comparator arm in all the trials was ADT alone in the form of orchidectomy, gonadotrophin-releasing hormone agonists and/or antagonists. ADT was administered continuously until disease progression or discontinuation of treatment.

Outcomes

The primary outcome of time to death due to the any cause was identified in all the included trials. Data were available in two trials for the predefined volume of metastasis subgroup ([Gravis 2013](#); [Sweeney 2015](#)), and we were able to obtain additional data from the authors of one trial for the type of metastasis subgroup ([Gravis 2013](#)). Only one study reported time to death due to prostate cancer ([James 2016](#)), so we instead analysed this as a dichotomous outcome for which all trials adequately reported data. We were able to obtain additional data from the authors of one trial for all the predefined subgroups for this outcome ([Gravis 2013](#)). The time-to-progression outcome was identified in all included trials, and one trial also provided additional data for both subgroups of interest ([Gravis 2013](#)). One trial reported toxicity data on a per-event basis ([Gravis 2013](#)), but we were able to contact the authors and obtain additional data to assess the toxicity outcomes of interest: grade III to V adverse events, all adverse events and discontinuation due to adverse events. We were unable to evaluate toxicity endpoints in other trials because they either did not report the events for the control arm of the trial ([Sweeney 2015](#)), or did not separately report events for the group of participants with metastatic disease ([James 2016](#)). Quality-of-life data were available in two studies ([Gravis 2013](#); [Sweeney 2015](#)), but one did not report adequate data to permit analysis ([Gravis 2013](#)).

Funding sources and conflicts of interest

All three included trials reported receiving funding from multiple sources including pharmaceutical companies and governments ([Gravis 2013](#); [James 2016](#); [Sweeney 2015](#)). Conflicts of interests with pharmaceutical companies were reported in all studies.

Excluded studies

We excluded one publication because it contained the wrong population ([Hassani 2017](#)): it was a very small trial of only 30 participants (total), of which only 14 participants across both arms had metastatic disease, which was an inclusion criterion. There was no stratification for disease stage and results were not separately reported for this subgroup. Therefore, we excluded this study.

Risk of bias in included studies

Detailed results of the 'Risk of Bias' assessment are provided in [Figure 2](#), and the judgements for individual domains are provided in the [Characteristics of included studies](#) table.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias): Time-to-death due to any cause	Blinding of outcome assessment (detection bias): Grade III to V adverse events	Blinding of outcome assessment (detection bias): Time-to-death due to prostate cancer	Blinding of outcome assessment (detection bias): Time-to-progression	Blinding of outcome assessment (detection bias): Discontinuation due to adverse events	Blinding of outcome assessment (detection bias): All adverse events	Blinding of outcome assessment (detection bias): Quality of life	Incomplete outcome data (attrition bias): Oncological outcomes	Incomplete outcome data (attrition bias): Toxicity outcomes	Incomplete outcome data (attrition bias): Quality of life	Selective reporting (reporting bias)	Other bias
Gravis 2013	+	+	-	+	-	-	?	?	-	-	+	+	-	+	+
James 2016	+	+	-	+	-	+	?	?	-	+	+	+	+	+	+
Sweeney 2015	+	+	-	+	-	?	-	?	-	-	+	+	-	+	+

Allocation

Random sequence generation

We rated all trials as having low risk of bias because computer algorithms were used in all studies.

Allocation concealment

We rated all trials as having low risk of bias because allocation was performed centrally in all studies.

Blinding

Blinding of participants and personnel

We rated all trials as having high risk of bias because neither participants or personnel were blinded in all studies.

Blinding of outcome assessment

- Time to death due to any cause: we rated all trials as having low risk of bias because blinding was unlikely to influence the outcome in any of the studies.
- Grade III to V adverse events: we rated all trials as having high risk of bias because unblinded investigators were responsible for grading the severity of events in all studies.
- Prostate cancer-specific death: we rated the risk of bias to be low where cause of death was determined by masked central review (James 2016), high where cause of death was determined by an unblinded investigator (Gravis 2013), and unclear where no information was provided (Sweeney 2015).
- Time to progression: we rated the risk of bias to be low where progression was measured objectively (PSA rise or radiological progression by RECIST) (Gravis 2013), high where clinical progression was determined by an unblinded investigator (Sweeney 2015), and unclear where it was unclear whether radiologists were aware of treatment group/trial participation when determining progression (James 2016).
- Discontinuation due to adverse events: we rated two studies as having unclear risk of bias because it was unclear whether assessors of reason for discontinuation were blinded (James 2016; Sweeney 2015). We judged the remaining study to be at high risk of bias, as it was likely that the assessor determining the reason for discontinuation was not blinded (Gravis 2013).
- All adverse events: we rated all trials as having high risk of bias because unblinded investigators were responsible for grading the severity of events in all studies.
- Quality of life: we rated two studies as being at high risk of bias because unblinded participants were rating their own quality of life (Gravis 2013; Sweeney 2015). This outcome was not assessed in James 2016.

Incomplete outcome data

- We rated all trials as being at low risk of bias for the following outcomes, because the vast proportion of participants

randomized were included in the analyses: time to death due to any cause; grade III to V adverse events; prostate cancer-specific death; time to progression; discontinuation due to adverse events; all adverse events.

- Quality of life: we rated two studies as having high risk of bias because only 41.6% and 77.0% of participants completed the 12-month quality-of-life assessment (Gravis 2013; Sweeney 2015). This outcome was not assessed in James 2016.

Selective reporting

We rated two studies as being at low risk of bias (Gravis 2013; James 2016), and one as being at high risk of bias (Sweeney 2015).

Other potential sources of bias

We rated all trials as having low risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Early taxane-based chemotherapy and androgen deprivation therapy (ADT) compared to ADT only for metastatic hormone-sensitive prostate cancer

1. Early taxane-based chemotherapy in combination with androgen deprivation therapy versus androgen deprivation therapy alone**1.1 Time to death due to any cause**

We included three randomized trials with 2,261 participants. Early taxane-based chemotherapy with androgen deprivation therapy (ADT) probably prolongs time to death due to any cause compared to ADT alone (hazard ratio (HR) 0.77, 95% confidence interval (CI) 0.68 to 0.87) (Figure 3). Compared to the five-year event rate in the control arms of the CHAARTED trial (Sweeney 2015), early treatment with taxane-based chemotherapy results in 94 fewer deaths from all causes per 1,000 (95% CI 137 fewer to 51 fewer). We rated the certainty of this evidence as moderate (Analysis 1.1).

Figure 3. Forest plot of comparison: 1 Overall Metastatic Population, outcome: 1.1 Time to death due to any cause.

1.2 Grade III to V adverse events

We included one study with 375 participants (Gravis 2013). Early taxane-based chemotherapy with ADT may increase the risk of

grade III to V adverse events compared to ADT alone (risk ratio (RR) 2.98, 95% CI 2.19 to 4.04) (Figure 4). This corresponds to 405 more grade III to V adverse events per 1,000 (95% CI 243 more to 621 more) in patients receiving early taxane-based chemotherapy with

ADT compared to those receiving ADT alone. We rated the certainty of this evidence as low ([Analysis 1.2](#)).

Figure 4. Forest plot of comparison: 1 Overall Metastatic Population, outcome: 1.2 Grade III to V adverse events.

1.3 Time to death due to prostate cancer (analyzed as prostate-cancer specific death)

We intended to analyze prostate cancer-specific survival as a time-to-event outcome, however this data was only available in two trials ([Gravis 2013](#); [James 2016](#)) so we instead decided to evaluate this as a dichotomous outcome as pre-specified in the protocol because data was available in all three included trials.

We included three randomized trials with 2,261 participants. Early taxane-based chemotherapy with ADT probably reduces the risk of prostate cancer-specific death compared to ADT alone (RR 0.79, 95% CI 0.70 to 0.89) ([Figure 5](#)). Compared to the prostate cancer-specific deaths in the GETUG-AFU15 trial ([Gravis 2013](#)), early treatment with taxane-based chemotherapy results in 108 fewer cancer-specific deaths per 1,000 (95% CI 154 fewer to 56 fewer). We rated the certainty of this evidence as moderate ([Analysis 1.3](#)).

Figure 5. Forest plot of comparison: 1 Overall Metastatic Population, outcome: 1.3 Prostate cancer-specific death.

1.4 Time to progression

We included three randomized trials with 2,261 participants. Early taxane-based chemotherapy with ADT probably delays disease progression compared to ADT alone (HR 0.63, 95% CI 0.56 to 0.71) ([Figure 6](#)). Compared to the baseline five-year progression event

rate obtained from the control arm of the CHAARTED trial ([Sweeney 2015](#)), early treatment with taxane-based chemotherapy results in 159 fewer incidences of disease progression per 1,000 (95% CI 202 fewer to 116 fewer). We rated the certainty of this evidence as moderate ([Analysis 1.4](#)).

Figure 6. Forest plot of comparison: 1 Overall Metastatic Population, outcome: 1.4 Time to progression.

1.5 Discontinuation due to adverse events

We included one study with 375 participants (Gravis 2013). Early taxane-based chemotherapy with ADT may result in a large increase in treatment discontinuation due to adverse events compared to ADT alone (RR 79.41, 95% CI 4.92 to 1282.78) (Analysis 1.5). This corresponds to 41 more events of treatment discontinuation per 1,000 (95% CI 25 more to 1000 more) in patients receiving early taxane-based chemotherapy with ADT compared to ADT alone. We rated the certainty of this evidence as low.

1.6 All adverse events

We included one study with 375 participants (Gravis 2013). Early taxane-based chemotherapy with ADT may increase the risk of adverse events of any grade compared to ADT alone (RR 1.11, 95% CI 1.06 to 1.17) (Analysis 1.6). This corresponds to 99 more adverse events of any grade per 1,000 (95% CI 54 more to 153 more) in patients receiving early taxane-based chemotherapy with ADT compared to ADT alone. We rated the certainty of this evidence as low.

1.7 Quality of life

We included one trial with 790 participants which measured quality of life with the Functional Assessment of Cancer Therapy-Prostate (FACT-P) scale, where a higher score is better. Early taxane-based chemotherapy with ADT may result in a small effect that may not be an important improvement in quality of life compared to ADT alone at 12 months (mean difference (MD) 2.85, 95% CI 0.13 to 5.57) (Analysis 1.7). We rated the certainty of this evidence as low.

Subgroup analysis

1. Volume of metastasis: high versus low

Time to death due to any cause

For high-volume disease the overall survival HR was 0.67 (95% CI 0.56 to 0.82), and for low-volume disease the HR was 1.03 (95% CI 0.77 to 1.38) (Analysis 2.1). The test for interaction was significant ($P = 0.02$, $I^2 = 82.5\%$).

Grade III to V adverse events

The RR of grade III to V adverse events with early taxane-based chemotherapy in addition to ADT was 2.72 (95% CI 1.81 to 4.07) for

high-volume disease, and 3.29 (95% CI 2.07 to 5.24) for low-volume disease (Analysis 2.2). The test for interaction was not significant ($P = 0.54$, $I^2 = 0\%$).

Prostate cancer-specific death

The RR of prostate cancer-specific death with early taxane-based chemotherapy in addition to ADT was 0.87 (95% CI 0.72 to 1.06) for high-volume disease and 0.79 (95% CI 0.54 to 1.16) for low-volume disease (Analysis 2.3). The test for interaction was not significant ($P = 0.65$, $I^2 = 0\%$).

Time to progression

The HR for time to progression was 0.58 (95% CI 0.49 to 0.69) for high-volume disease, and 0.73 (95% CI 0.60 to 0.91) for low-volume disease (Analysis 2.4). The test for interaction was not significant ($P = 0.09$, $I^2 = 65.6\%$).

Discontinuation due to adverse events

The RR of discontinuation due to adverse events with early taxane-based chemotherapy in addition to ADT was 38.58 (95% CI 2.36 to 629.57) for high-volume disease, and 41.81 (95% CI 2.56 to 682.07) for low-volume disease (Analysis 2.5). The test for interaction was not significant ($P = 0.97$, $I^2 = 0\%$).

All adverse events

The RR of all adverse events with early taxane-based chemotherapy in addition to ADT was 1.14 (95% CI 1.05 to 1.24) for high-volume disease, and 1.09 (95% CI 1.02 to 1.16) for low-volume disease (Analysis 2.6). The test for interaction was not significant ($P = 0.38$, $I^2 = 0\%$).

Quality of life

The MD for quality of life at 12 months with early taxane-based chemotherapy in addition to ADT was 4.30 (95% CI -0.42 to 9.02) for high-volume disease, and 1.00 (95% CI -4.42 to 6.42) for low-volume disease (Analysis 2.7). The test for interaction was not significant ($P = 0.37$, $I^2 = 0\%$).

2. Type of metastases: nodal only versus visceral, bone and/or nodal metastases

Time to death due to any cause

The HR for time to death due to any cause for nodal metastases only was 1.04 (95% CI 0.40 to 2.69) and 0.82 (95% CI 0.63 to 1.08) for all other types of metastases (Analysis 3.1). The test for interaction was not significant ($P = 0.64$, $I^2 = 0\%$).

Grade III to V adverse events

The RR of grade III to V adverse events with early taxane-based chemotherapy in addition to ADT was 6.54 (95% CI 2.16 to 19.85) for nodal metastases only, and 2.67 (95% CI 1.95 to 3.67) for all other types of metastases (Analysis 3.2). The test for interaction was not significant ($P = 0.13$, $I^2 = 56.7\%$).

Prostate cancer-specific death

The RR of prostate cancer-specific death with early taxane-based chemotherapy in addition to ADT was 0.83 (95% CI 0.38 to 1.82) for nodal metastases only, and 0.85 (95% CI 0.70 to 1.03) for all other types of metastases (Analysis 3.3). The test for interaction was not significant ($P = 0.95$, $I^2 = 0\%$).

Time to progression

The HR for time to progression was 0.84 (95% CI 0.42 to 1.66) for nodal metastases only, and 0.65 (95% CI 0.51 to 0.83) for all other types of metastases (Analysis 3.4). The test for interaction was not significant ($P = 0.50$, $I^2 = 0\%$).

Discontinuation due to adverse events

The RR of discontinuation due to adverse events with early taxane-based chemotherapy in addition to ADT was 11.34 (95% CI 0.65 to 196.88) for nodal metastases only, and 69.00 (95% CI 4.27 to 1115.90) for all other types of metastases (Analysis 3.5). The test for interaction was not significant ($P = 0.34$, $I^2 = 0\%$).

All adverse events

The RR of all adverse events with early taxane-based chemotherapy in addition to ADT was 1.10 (95% CI 0.97 to 1.26) for nodal metastases only, and 1.11 (95% CI 1.06 to 1.18) for all other types of metastases (Analysis 3.6). The test for interaction was not significant ($P = 0.90$, $I^2 = 0\%$).

Quality of life

We were unable to perform a subgroup analysis due to there being insufficient data.

DISCUSSION

Summary of main results

We included three randomized controlled trials with 2,261 participants (Table 1; Table 2). Compared to androgen deprivation therapy (ADT) alone, the early addition of taxane-based chemotherapy to ADT for metastatic hormone-sensitive prostate cancer probably improves both overall and disease-specific survival and reduces disease progression. Taxane-based chemotherapy in addition to ADT may increase toxicity compared to ADT alone. The addition of taxane-based chemotherapy may result in a small improvement in quality of life 12 months after diagnosis of metastases, though this effect may not be clinically

important. The treatment effect may be greater for participants with high-volume disease than for those with low-volume disease, but the included studies were mostly not designed nor powered to assess for subgroup effects

Overall completeness and applicability of evidence

- This review included three randomized trials consisting of men with metastatic hormone-sensitive prostate cancer who had a variety of clinical histories (e.g. prior local therapy, adjuvant ADT), which reflects the population encountered in routine clinical practice.
- The majority of included participants had newly diagnosed metastatic prostate cancer and thus we are uncertain whether the treatment effect is the same for those with prior local treatment, although there is currently no evidence to suggest otherwise.
- The only taxane-based chemotherapy agent used in the trials was docetaxel and thus we do not know whether other taxanes (e.g. cabazitaxel) have the same treatment effect.
- We were unable to analyze time to prostate-cancer-specific death as a time-to-event outcome because of insufficient data. We instead analyzed this as a dichotomous outcome, but we will endeavour to analyze this outcome as initially planned in future updates if data become available.
- It was challenging to analyze adverse event outcomes in this review because of insufficient and heterogeneous reporting of data, which is a concern for reporting bias. Furthermore, our confidence in the estimates was lowered due to imprecision and study limitations pertaining to performance and detection bias. However, the results suggest that there is likely an increased risk of adverse events with the addition of taxane-based chemotherapy to ADT. The most common adverse events experienced with taxane-based chemotherapy treatment in addition to ADT were fatigue, anaemia and alopecia, each of which were each experienced by the majority of participants (Gravis 2013).
- The improvement in quality of life with the addition of early docetaxel to ADT appears to be small and may not be clinically significant (Cella 2009), but there were important study limitations pertaining to detection, performance and attrition bias which may affect this estimate.
- It will be important to assess the comparative effectiveness of taxane-based chemotherapy to other agents, which have been shown to be effective treatments for men with hormone-sensitive prostate cancer, for example, abiraterone acetate (Fizazi 2017; James 2017).

Quality of the evidence

We consistently downgraded our assessments of the certainty of the evidence by one or two steps, to moderate or low. Our confidence in the estimates of effect was lowered due to study limitations (issues surrounding allocation concealment and blinding), inconsistency (high I^2 values which we were unable to explain through secondary analysis), imprecision (wide confidence intervals that crossed the assumed threshold of clinically important difference, or were due to few events), or a combination of these factors.

We classified all trials as being at high risk of performance bias because neither the participants or the personnel were blinded

to the treatment allocation. This could have led to differential treatment of participants, for example increased frequency of radiological imaging or application of a lower clinical threshold to commence further life-prolonging therapies, due to the knowledge that the participant was not receiving docetaxel.

Potential biases in the review process

Despite a comprehensive search strategy without any publication or language restrictions, there is a possibility that we may have missed studies published in a language other than English, published in non-indexed journals or not published at all. The number of studies included in this review was insufficient to generate funnel plots; therefore, we may have underestimated the risk of publication bias. We contacted study authors on several occasions, and they provided feedback to some of our queries but only one (Gravis 2013) provided the additional data we requested and this may represent a source of bias.

Agreements and disagreements with other studies or reviews

We have identified three other systematic reviews on the same research question (Botrel 2016; Tucci 2016; Vale 2016), although the latter also included participants with localized disease and included bisphosphonates as an intervention. None of these reviews applied the same rigorous methodology as this Cochrane Review, which includes a published protocol, a focus on outcomes important to patients, an exhaustive literature search and an assessment of the quality of evidence using the GRADE framework. The findings from our review are consistent with the other reviews, that is, that the addition of taxane-based chemotherapy to ADT prolongs survival and delays disease progression. Unlike our review, Botrel and colleagues analysed adverse events on an individual basis and reported that combination treatment with docetaxel and ADT may increase the risk of neutropenia, febrile neutropenia and fatigue (Botrel 2016). There was no difference between the groups for other adverse events. Our review also found that treatment with docetaxel in addition to ADT may increase the risk of grade III to V adverse events.

AUTHORS' CONCLUSIONS

Implications for practice

Early taxane-based chemotherapy in addition to androgen deprivation therapy (ADT) was shown to probably improve both overall and disease-specific survival, and to reduce disease progression in those with metastatic, hormone-sensitive prostate cancer. It is important that clinicians counsel patients regarding the increased risk of grade III to V adverse events when adding taxane-based chemotherapy to the treatment regimen compared to ADT alone, and that they take this factor into consideration when making decisions regarding management. Furthermore, it is imperative that individuals are aware of the lack of high-quality evidence regarding changes to quality of life in this setting; any

benefit of commencing taxane-based chemotherapy early with ADT for this outcome may only be small and clinically unimportant compared to treatment with ADT only.

Implications for research

Given the low to moderate certainty of evidence that characterizes most of the reported analyses, future trials should strive for higher methodological standards with regards to blinding to minimize concerns about performance and detection bias. However, we acknowledge that it is probably not feasible to blind both participants and personnel in this particular setting for all outcomes. Furthermore, we experienced difficulty in analyzing adverse effects because of inadequate and heterogeneous reporting in published articles; this suggests that a framework for reporting toxicity in manuscripts should be developed and implemented by journals to ensure consistency and comparability between studies.

As our subgroup analysis found that the treatment effect may be greatest in patients with high-volume disease (Gravis 2018; Kyriakopoulos 2018) — and that there may only be a small effect, if any, for those with low-volume metastases — it is important for future studies to be designed to specifically explore whether there is a difference in effect based on the volume of disease.

Similarly, it is important that future trials assess quality-of-life in detail, as it is a patient-important outcome and the current evidence does not facilitate a confident estimate of treatment effect. Additionally, adequately powered future studies are required to characterize treatment effect for subgroups of patient characteristics, for example, the volume of metastasis, the type of metastasis and the receipt of prior local therapy, because the effect of treatment may not be comparable between these groups (Gravis 2018).

Two recent trials have suggested that abiraterone acetate also improves outcomes compared to ADT alone (Fizazi 2017; James 2017); and therefore, trials are required to compare early taxane-based chemotherapy and early abiraterone acetate in this clinical setting to characterize whether there is a difference in treatment effect between the two agents.

Another important consideration is to assess whether the results observed represent a true benefit or whether it is due to lead-time bias. Therefore, future research should attempt to characterize whether there is a difference in early versus deferred treatment.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Gravis 2013

Methods	Study design: open label, randomized controlled, parallel-group trial Setting/country: 29 centers in France and 1 in Belgium, not further specified. Dates when study was conducted: randomization from October 2004 to December 2008
Participants	Inclusion criteria <ul style="list-style-type: none"> Prostate adenocarcinoma, proven histologically. Measurable or assessable metastatic disease. Absence of previous chemotherapy for the metastatic prostate cancer. Chemotherapy in an adjuvant or neoadjuvant situation or for elevation of PSA is accepted if it was ended more than a year previously, with evidence of absence of progress on the PSA or of appearance of metastases for more than a year.

Gravis 2013 (Continued)

- Adjuvant or neoadjuvant hormone therapy or hormone therapy for elevation of PSA is accepted if it was ended more than a year previously, with evidence of absence of progress on the PSA or of appearance of metastases for more than a year.
- Hormone therapy for the metastatic disease may have started but must not have been administered for more than 2 months on inclusion in the trial.
- Any radiotherapy on the sites of metastases must have been completed at the time of inclusion in the trial.

Exclusion criteria

- Severe cardiovascular disease (symptomatic coronary disease, congenital heart failure, classes 3 and 4 of the NYHA classification).
- Severe peripheral neuropathy.
- Active infection or other serious underlying disease which may prevent the patient from receiving the treatment.
- A history of cancer in the 5 years prior to inclusion in the study, other than treated baso-cellular cutaneous cancer.
- Patients who have had surgical castration.
- Symptomatic or asymptomatic cerebral metastases which are not under control.

Total number of participants randomly assigned: 385

Group A (Docetaxel + ADT)

- Number of all participants randomly assigned: 192
- Age: 63 (IQR 57 to 68)
- Previous local treatment: 32%
- PSA: 26.7 (5 to 106)
- High-volume metastatic disease: 47%

Group B (ADT only)

- Number of all participants randomly assigned: 193
- Age: 64 (IQR 58 to 70)
- Previous local treatment: 24%
- PSA: 25.8 (5 to 127)
- High-volume metastatic disease: 48%

Interventions

Group A: Docetaxel (75 mg/m²/day on Day 1 every 3 weeks, continued if the patient responds or is stable for a maximum of 9 cycles) and androgen deprivation therapy (LHRH agonist, surgical castration or complete androgen blockade)

Group B: androgen deprivation therapy (LHRH agonist, surgical castration or complete androgen blockade)

Duration: docetaxel administered for 9 cycles; ADT administered until the development of androgen resistance

ADT with early docetaxel

Outcomes
Primary outcome

- To compare the benefit for overall survival at 36 months of docetaxel + androgen blockade as first-line treatment of metastatic prostate cancers versus androgen blockade on its own.

Timepoints reported: median survival reported and Kaplan-Meier curve demonstrates survival at 12 monthly intervals up to 60 months from randomization.

Secondary outcomes

- To compare survival without progression in laboratory or clinical terms at 24 months

Gravis 2013 (Continued)

- To compare quality of life
- To compare the tolerability of the treatments

How measured: PSA and radiological imaging was used to measure progression; EORTC QLQ-C30 core questionnaire was used for quality of life.

Timepoints measured: every 3 months for 3.5 years then every 6 months until progression; quality-of-life questionnaire was administered to Group A at inclusion, day 1 on cycle 4, day 21 on cycle 9 and then every 6 months, and to Group B at inclusion, 3 months and then every 6 months.

Timepoints reported: median progression-free survival reported and Kaplan-Meier curve demonstrates survival at 12-monthly intervals up to 60 months from randomization; quality-of-life outcomes reported at baseline, month 3, 6 and 12.

Safety outcomes

How measured: CTC-NCI scale (version 3.0).

Timepoints measured: at each visit.

Timepoints reported: at each visit.

Subgroup: a post-hoc analysis was conducted based on the volume of metastases.

Funding sources	French Health Ministry and Institut National du Cancer (PHRC), Sanofi-Aventis, AstraZeneca and Amgen.
Declarations of interest	Authors have been speakers, received honoraria, received research grants and/or participated in advisory boards for AstraZeneca, Sanofi Aventis, Amgen, Novartis, Keocyt, Ipsen, Janssen, Astellas and Medivation, Bristol-Myers Squibb, Algeta, Bayer.
Notes	Language of publication: English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly allocated in a 1:1 ratio to receive ADT plus docetaxel or ADT alone. Dynamic minimization was used to minimize the imbalance of three criteria: previous systemic treatment with ADT; chemotherapy for local disease or isolated rising PSA; and Glass risk groups.
Allocation concealment (selection bias)	Low risk	Centralised allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Both participants and personnel unblinded
Blinding of outcome assessment (detection bias) Time-to-death due to any cause	Low risk	Blinding unlikely to influence outcome
Blinding of outcome assessment (detection bias) Grade III to V adverse events	High risk	Unblinded investigators are responsible for grading severity of adverse event.
Blinding of outcome assessment (detection bias)	High risk	"Causes of death were reported by [unblinded] investigators rather than by central review"

Gravis 2013 (Continued)

Time-to-death due to
prostate cancer

Blinding of outcome assessment (detection bias) Time-to-progression	Unclear risk	Unclear whether radiologists were aware of treatment allocation
Blinding of outcome assessment (detection bias) Discontinuation due to adverse events	Unclear risk	Not specified whether assessor reviewing reason for discontinuing treatment was blinded
Blinding of outcome assessment (detection bias) All adverse events	High risk	Unblinded investigators are responsible for classifying, grading and reporting an adverse event.
Blinding of outcome assessment (detection bias) Quality of life	High risk	Unblinded patients rating their own QoL.
Incomplete outcome data (attrition bias) Oncological outcomes	Low risk	Vast proportion of patients randomized included in analysis for this outcome (188/192 in ADT plus docetaxel arm; 190/193 in ADT arm).
Incomplete outcome data (attrition bias) Toxicity outcomes	Low risk	Vast proportion of patients randomized included in analysis for this outcome (189/192 in ADT plus docetaxel arm; 186/193 in ADT arm).
Incomplete outcome data (attrition bias) Quality of life	High risk	Only 160 QoL responses at 12 months overall and no description as to the numbers in each group
Selective reporting (reporting bias)	Low risk	Appears all outcomes outlined in the protocol (Section 9) have been reported in the prespecified way.
Other bias	Low risk	None detected.

James 2016

Methods	<p>Study design: open label, randomized controlled, parallel-group trial</p> <p>Setting/country: 120 centres across the UK and Switzerland, not further specified.</p> <p>Dates when study was conducted: randomization from Oct 2005 and March 2013</p>
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> Histologically confirmed prostate adenocarcinoma. High-risk newly diagnosed non-metastatic node-negative disease (at least two of stage T3/4, PSA $\geq$ 40 ng/ml or Gleason sum score 8 to 10, intention to treat with radical radiotherapy) or Newly diagnosed metastatic or node-positive disease (N+ and/or M+) or previously treated with local therapy and now relapsing (at least one of PSA $\geq$ 4 ng/ml and rising with doubling time less than 6 months, PSA $\geq$ 20 ng/ml, N+ or M+). Intention to treat with long-term androgen deprivation therapy. Fit for all protocol treatment 2 and follow-up, WHO performance status 0 to 2. <p>Exclusion criteria</p>

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- Prior systemic therapy for locally advanced or metastatic prostate cancer.
- Metastatic brain disease or leptomeningeal disease.
- Abnormal liver functions consisting of any of the following: serum bilirubin $\geq 1.5 \times \text{ULN}$ (except for patients with Gilbert's disease, for whom the upper limit of serum bilirubin is $51.3 \mu\text{mol/l}$ or 3mg/dl); aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\geq 2.5 \times \text{ULN}$.
- Any other previous or current malignant disease which, in the judgement of the responsible physician, is likely to interfere with STAMPEDE treatment or assessment.
- Patients with active peptic ulceration, gastrointestinal bleeding, inflammatory bowel disease.
- Symptomatic peripheral neuropathy grade < 2 .
- Any surgery (e.g. TURP) performed within the past 4 weeks.
- Patients with significant cardiovascular disease such that, in the investigator's opinion, the patient is unfit for any of the study treatments.
- Patients who have been scheduled to have major dental extractions within the next 2 years.
- Patients receiving treatment with drugs known to induce CYP3A4.
- Prior exposure to abiraterone.
- Prior chemotherapy for prostate cancer.
- Prior therapy with zoledronic acid other than short-term treatment for hypercalcaemia.

Total number of participants randomly assigned: 2,962 (1,086 met the inclusion criteria for our review)

Group A (Docetaxel + ADT)

- Number of all participants randomly assigned: 592 (362 had metastatic disease)
- Median age: 65 (IQR 61 to 71)
- Median PSA: 70 (IQR 27 to 181)
- Metastatic patients: 61%
- Previous local therapy (amongst metastatic patients): 4.1%

Group B (ADT only)

- Number of all participants randomly assigned: 1,184 (724 had metastatic disease)
- Median age: 65 (IQR 60 to 70)
- Median PSA: 67 (IQR 23 to 200)
- Metastatic patients: 61%
- Previous local therapy (amongst metastatic patients): 4.7%

Interventions

Group A: docetaxel (75 mg per square meter of body-surface area given every 3 weeks for up to six cycles) and androgen deprivation therapy (LHRH agonists or antagonists, bilateral orchidectomy, combined androgen blockade).

Group B: docetaxel (75 mg per square meter of body-surface area given every 3 weeks for up to six cycles), zoledronic acid (zoledronate IV 4mg every 3 weeks for 6 courses and then every 4 weeks for up to 2 years in the absence of disease progression or unacceptable toxicity) and androgen deprivation therapy (LHRH agonists or antagonists, bilateral orchidectomy, combined androgen blockade).

Group C: androgen deprivation therapy (LHRH agonists or antagonists, bilateral orchidectomy, combined androgen blockade).

Duration: docetaxel given for up to six cycles, zoledronic acid up to 2 years and androgen deprivation therapy until disease progression.

Outcomes

Primary outcome

- Overall survival

Timepoints reported: survival reported as a continuous outcome with medians and Kaplan-Meier curves.

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Secondary outcomes

- Failure-free survival
- Biochemical failure
- Compare the safety of androgen suppression (AS) alone versus AS in varying combinations with zoledronate and docetaxel in patients with locally advanced or metastatic prostate cancer
- Progression-free survival
- Disease-specific survival

How measured: progression measured by PSA test, radiological tests and cause of death.

Timepoints measured: at each visit.

Timepoints reported: survival reported as a continuous outcome with medians and Kaplan-Meier curves.

Safety outcomes

How measured: Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Timepoints measured: at each visit.

Timepoints reported: at each visit.

Funding sources	Cancer Research UK, Medical Research Council, Novartis, Sanofi-Aventis, Pfizer, NIHR Clinical Research Network, Swiss Group for Clinical Cancer Research
Declarations of interest	GA reports personal fees from Sanofi -Aventis; personal fees and non-financial support from Astellas; personal fees from Novartis; grants, personal fees, and non-financial support from Janssen, personal fees and non-financial support from Roche/Ventana, personal fees and non-financial support from Medivation, personal fees from Millennium Pharmaceuticals, personal fees and non-financial support from Abbott Laboratories, personal fees from Essa Pharmaceuticals, personal fees and non-financial support from Bayer Healthcare Pharmaceuticals, personal fees from Takeda, and grants from AstraZeneca. AJB reports other support from Janssen, Sanofi, and Astellas, outside the submitted work. RC reports personal fees as a Consultant for Sanofi -Aventis, outside the submitted work. SC reports grants and personal fees from Sanofi-Aventis, outside the submitted work. JdB reports advisory boards and paid participation for Sanofi -Aventis. DPD reports grants from Cancer Research UK, during the conduct of the study; personal fees from Takeda Pharmaceuticals, outside the submitted work. TE reports that patients entering this study received docetaxel free of charge (Sanofi) and has previously received per-patient payment for entering patients in other commercial trials investigating docetaxel. JDG reports other support as a local principal investigator for a study of radium-223 in prostate cancer funded by Bayer, and other support as a local principal investigator for a study of LHRH antagonist in prostate cancer funded by Millennium Pharmaceuticals, outside the submitted work. NDJ reports grants and personal fees from Sanofi, and grants and personal fees from Novartis, during the conduct of the study; grants and personal fees from Janssen, grants and personal fees from Astellas, and grants and personal fees from Bayer, outside the submitted work. RJJ reports grants from Sanofi, and grants and non-financial support from Novartis, during the conduct of the study; grants, personal fees, and non-financial support from Sanofi, grants, personal fees, and non-financial support from Novartis, outside the submitted work. MDM reports personal fees from Sanofi, personal fees from Bayer, personal fees from Dendreon, personal fees from Bristol-Myers, and personal fees from Janssen, outside the submitted work. CCP reports personal fees from Sanofi -Aventis, research funding and speaker's honoraria from Bayer, and Bavarian Nordic and Janssen, outside the submitted work. MKBP reports funding from Cancer Research UK, Medical Research Council, Novartis, Sanofi -Aventis, Pfizer, Janssen, Astellas, NIHR Clinical Research Network (formerly National Cancer Research Network), and SAKK—Swiss Group for Clinical Cancer Research, during the conduct of the study. JMR reports personal fees from Janssen (lecture fee), outside the submitted work. MRSp reports grants and non-financial support from Sanofi -Aventis, grants and non-financial support from Novartis, grants and non-financial support from Pfizer, grants and non-financial support from Janssen, and grants and non-financial support from Astellas, during the conduct of the study. JS reports support for travel and speakers fees for the following companies in the field of prostate cancer, not related to this paper: Janssen Bayer and Astellas. SS reports personal fees and non-financial support from Sanofi -Aventis, outside the submitted work. MRSy

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Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomized centrally using a computerized algorithm.
Allocation concealment (selection bias)	Low risk	Randomization performed centrally
Blinding of participants and personnel (performance bias) All outcomes	High risk	Both unblinded; study described as open label
Blinding of outcome assessment (detection bias) Time-to-death due to any cause	Low risk	Blinding not likely to influence outcome
Blinding of outcome assessment (detection bias) Grade III to V adverse events	High risk	Severity graded by investigator who was not blinded
Blinding of outcome assessment (detection bias) Time-to-death due to prostate cancer	Low risk	Cause of death was determined by masked central review
Blinding of outcome assessment (detection bias) Time-to-progression	Unclear risk	Unclear whether radiologists were aware of treatment group/trial participation when determining progression
Blinding of outcome assessment (detection bias) Discontinuation due to adverse events	Unclear risk	Unclear whether assessors of reason for discontinuation were blinded
Blinding of outcome assessment (detection bias) All adverse events	High risk	Investigator who was unblinded had to determine severity and causality
Blinding of outcome assessment (detection bias) Quality of life	Low risk	Not applicable

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Incomplete outcome data (attrition bias) Oncological outcomes	Low risk	All randomized participants included in the analyses for each arm for this outcome
Incomplete outcome data (attrition bias) Toxicity outcomes	Low risk	Vast proportion of participants randomized included in analysis for this outcome (550/552 in ADT plus docetaxel arm; 516/593 in ADT plus docetaxel plus zoledronic acid; 1128/1184 in ADT arm).
Incomplete outcome data (attrition bias) Quality of life	Low risk	Not applicable
Selective reporting (reporting bias)	Low risk	Outcomes outlined in Table 1 of protocol are reported in the manuscript as preplanned
Other bias	Low risk	None detected

Sweeney 2015

Methods	<p>Study design: open label, randomized controlled, parallel-group trial</p> <p>Setting/country: institutions in the USA that are a part of the Eastern Cooperative Oncology Group, not further specified</p> <p>Dates when study was conducted: randomization from July 2006 through December 2012</p>
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> Patients must have histologically or cytologically confirmed prostate cancer. Patients may have begun hormonal therapy but it must not have commenced more than 120 days prior to randomization. Patients must have metastatic disease. Patients are not eligible if the PSA has risen and met criteria for progression. Patients must have discontinued hormonal therapy in the adjuvant or neoadjuvant setting (or both) 12 months prior to beginning protocol therapy, AND must not have exceeded 24 months of therapy AND have shown to have no evidence of disease (PSA < 0.1 ng/dL after prostatectomy plus hormonal therapy and < 0.5 ng/dL and not have doubled above nadir after radiation therapy plus hormonal therapy) at least 12 months after completing adjuvant or neoadjuvant hormonal therapy. Patients must have ECOG performance status of 0 to 2. <p>Exclusion criteria</p> <ul style="list-style-type: none"> Patients with prior chemotherapy in the adjuvant or neoadjuvant setting are ineligible. Prior history of malignancy in the past 5 years with the exception of basal cell and squamous cell carcinoma of the skin. Active cardiac disease defined as active angina, symptomatic congestive heart failure, or myocardial infarction within previous six months. Patients with prior hormone therapy in the metastatic setting. <p>Total number of participants randomly assigned: 790</p> <p>Group A (Docetaxel + ADT)</p> <ul style="list-style-type: none"> Number of all participants randomly assigned: 397 Age: 64 [range 36 to 88] Median PSA: 50.9 [range 0.2 to 8540] Prior local therapy: 27.2% High-volume metastatic disease: 66.2%

Sweeney 2015 (Continued)

Group B (ADT only)

- Number of all participants randomly assigned: 393
- Age: 63 [range 39 to 91]
- Median PSA: 52.1 [range 0.1 to 8056]
- Prior local therapy: 27.0%
- High-volume metastatic disease: 63.6%

Interventions

Group A: early docetaxel (at a dose of 75 mg per square meter of body-surface area given every 3 weeks for up to six cycles with premedication with 8 mg of oral dexamethasone at 12 hours, 3 hours, and 1 hour before docetaxel infusion) and androgen deprivation therapy (LHRH agonist or antagonist therapy, surgical castration or combined androgen blockade).

Group B: androgen deprivation therapy (LHRH agonist or antagonist therapy, surgical castration or combined androgen blockade).

Duration: up to 6 cycles of docetaxel; androgen deprivation therapy administered until progression.

Outcomes
Primary outcome

- To evaluate the ability of early chemotherapy to improve overall survival in men commencing androgen deprivation for metastatic prostate cancer.

Timepoints reported: survival reported as a continuous outcome with medians and Kaplan-Meier curves.

Secondary outcomes

- To determine whether early chemotherapy can increase the time to clinical progression (radiographic or symptomatic deterioration due to disease) over hormonal therapy alone.
- To determine whether early chemotherapy can increase the time to development of hormone refractory disease over hormonal therapy alone.
- To determine whether early chemotherapy can increase time to serological progression over hormonal therapy alone.
- To determine rates of biochemical response at 6 months and 12 months in the chemohormonal arm versus the hormonal therapy alone arm.
- To determine the frequency of adverse events and the tolerability of chemotherapy combined with hormonal therapy versus hormonal therapy alone.
- To determine whether the postulated clinically meaningful increase in disease control is associated with an alteration in overall quality of life using the Functional Assessment of Cancer Therapy-Prostate questionnaire (FACT-P, self-administered).
- To determine the ability of PSA changes to be a surrogate for clinical benefit from therapy and overall survival.

How measured: progression measured by clinical evaluation, PSA testing and radiological tests; FACT-P questionnaire used for quality of life.

Timepoints measured: progression measured for Group A every three weeks while receiving docetaxel then every 3 months; and every 3 months for Group B; quality of life measured at baseline then every 3 months for 12 months.

Timepoints reported: progression reported as a continuous outcome with medians and Kaplan-Meier curves; all quality-of-life timepoints reported.

Safety outcomes

How measured: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE; version 3.0 until September 2011 and version 4.0 thereafter).

Timepoints measured: at each visit.

Timepoints reported: at each visit.

Sweeney 2015 (Continued)

Subgroup: a post hoc analysis was conducted based on the volume of metastatic disease.

Funding sources	The National Cancer Institute, National Institutes of Health, Department of Health and Human Services, and by grants from the Public Health Service. Sanofi provided the docetaxel and a grant to ECOG-ACRIN.
Declarations of interest	Dr. Carducci reports personal fees from Sanofi, Amgen, Astellas, and Medivation outside the submitted work. Dr. DiPaola reports other support from Sanofi-Aventis during the conduct of the study. Dr. Dreicer reports personal fees from Millennium, Medivation, Astellas, Bind Pharmaceuticals, Genentech, Roche, and Dendreon outside the submitted work. Dr. Eisenberger reports personal fees from Sanofi outside the submitted work. Dr. Garcia reports grant support and personal fees from Astellas and Bayer, and personal fees from Sanofi outside the submitted work. Dr. Hahn reports grant support from Sanofi-Aventis during the conduct of the study; grant support from Dendreon, grant support and personal fees from OncoGeneX, grant and non-financial support from Millennium, and personal fees from Medivation and Sanofi-Aventis outside the submitted work. Dr. Hussain reports grant support from the SWOG during the conduct of the study. Dr. Liu reports grant support from the University of Wisconsin Carbone Cancer Center during the conduct of the study. Dr. Picus reports grant support from the National Cancer Institute during the conduct of the study. Dr. Sweeney reports grant support from the NCI during the conduct of the study, and personal fees from Sanofi, Janssen, Astellas, Bayer, and Genentech, personal fees and other support from BIND Therapeutics, and other support from Leuchemix outside the submitted work. In addition, Dr. Sweeney reports a patent related to the use of Pathenolide to inhibit cancer (US6890946 B2), issued to Indiana University, and a pending patent related to a Abiraterone plus Cabozantinib combination, held by Exelixis. Dr. Wong reports other support from Sanofi during the conduct of the study; grant support from Pfizer, Medivation, Millennium, and other support from outside the submitted work.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Protocol Appendix I: "a computer program will place you..." Protocol 9.5: permuted blocks
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participant and personnel unblinded; described as open label
Blinding of outcome assessment (detection bias) Time-to-death due to any cause	Low risk	Blinding unlikely to bias results
Blinding of outcome assessment (detection bias) Grade III to V adverse events	High risk	Unblinded investigators determined grade of severity of adverse events
Blinding of outcome assessment (detection bias) Time-to-death due to prostate cancer	Unclear risk	No information on whether assessors of cause of death were blinded

Sweeney 2015 (Continued)

Blinding of outcome assessment (detection bias) Time-to-progression	High risk	Clinical progression determined by unblinded investigator (Protocol 6.4.3)
Blinding of outcome assessment (detection bias) Discontinuation due to adverse events	Unclear risk	Unclear whether assessors of reason for discontinuation were blinded
Blinding of outcome assessment (detection bias) All adverse events	High risk	ADT-only events were not routinely reported. Investigators were unblinded and responsible for reporting events.
Blinding of outcome assessment (detection bias) Quality of life	High risk	Unblinded participants self-assessed quality of life.
Incomplete outcome data (attrition bias) Oncological outcomes	Low risk	All randomized patients included in the analyses for each arm for this outcome
Incomplete outcome data (attrition bias) Toxicity outcomes	Low risk	Vast proportion of participants randomized included in analysis for this outcome (390/397 in ADT plus docetaxel arm; 392/393 in ADT arm); see appendix (Figure S1).
Incomplete outcome data (attrition bias) Quality of life	High risk	A considerable proportion of randomized participants did not complete the 12-month QoL assessment: 83/368 in ADT plus docetaxel arm, and 83/353 in the ADT-only arm.
Selective reporting (reporting bias)	Low risk	Outcomes outlined in Table 1 of protocol are reported in the manuscript as preplanned
Other bias	Low risk	None detected.

ADT: androgen deprivation therapy

CTC-NCI: Common Toxicity Criteria-National Cancer Institute

CYP3A4: cytochrome P450 3A4

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients

LHRH: luteinising hormone releasing hormone

IQR: interquartile range

NYHA: New York Heart Association

PSA: prostate specific antigen

TURP: transurethral resection of the prostate

QoL: quality of life

ULN: upper limit of normal

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Hassani 2017	Wrong population: this was a very small trial of only 30 participants (total) of which only 14 participants across both arms had metastatic disease, which was an inclusion criterion. There was no stratification for disease stage and results were not reported separately for this subgroup. Therefore, we excluded this study.

DATA AND ANALYSES

Comparison 1. Overall Metastatic Population

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to death due to any cause	3		Hazard Ratio (Random, 95% CI)	0.77 [0.68, 0.87]
2 Grade III to V adverse events	1	375	Risk Ratio (M-H, Random, 95% CI)	2.98 [2.19, 4.04]
3 Prostate cancer-specific death	3	2261	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.70, 0.89]
4 Time to progression	3		Hazard Ratio (Random, 95% CI)	0.63 [0.56, 0.71]
5 Discontinuation due to adverse events	1	385	Risk Ratio (M-H, Random, 95% CI)	79.41 [4.92, 1282.78]
6 All adverse events	1	375	Risk Ratio (M-H, Random, 95% CI)	1.11 [1.06, 1.17]
7 Quality of life	1		Mean Difference (Random, 95% CI)	2.85 [0.13, 5.57]

Analysis 1.1. Comparison 1 Overall Metastatic Population, Outcome 1 Time to death due to any cause.

Study or subgroup	Taxane Chemother- apy + ADT	ADT only	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
Gravis 2013	0	0	-0.1 (0.129)		23.91%	0.87[0.67,1.12]
James 2016	0	0	-0.3 (0.1)		39.85%	0.76[0.63,0.93]
Sweeney 2015	0	0	-0.3 (0.105)		36.24%	0.72[0.59,0.88]
Total (95% CI)					100%	0.77[0.68,0.87]
Heterogeneity: Tau ² =0; Chi ² =1.28, df=2(P=0.53); I ² =0%						
Test for overall effect: Z=4.13(P<0.0001)						
				Taxane Chemotherapy + ADT 0.01 0.1 1 10 100 ADT only		

Analysis 1.2. Comparison 1 Overall Metastatic Population, Outcome 2 Grade III to V adverse events.

Study or subgroup	Taxane Chemother- apy + ADT	ADT only	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Gravis 2013	n/N 115/189	n/N 38/186		100%	2.98[2.19,4.04]
Total (95% CI)	189	186		100%	2.98[2.19,4.04]
Total events: 115 (Taxane Chemotherapy + ADT), 38 (ADT only)					
				Taxane Chemotherapy + ADT 0.01 0.1 1 10 100 ADT only

Analysis 1.3. Comparison 1 Overall Metastatic Population, Outcome 3 Prostate cancer-specific death. **Analysis 1.4. Comparison 1 Overall Metastatic Population, Outcome 4 Time to progression.** **Analysis 1.5. Comparison 1 Overall Metastatic Population, Outcome 5 Discontinuation due to adverse events.**

Analysis 1.6. Comparison 1 Overall Metastatic Population, Outcome 6 All adverse events.

Analysis 1.7. Comparison 1 Overall Metastatic Population, Outcome 7 Quality of life.

Comparison 2. Volume of Metastases Subgroup

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Time to death due to any cause	2		Hazard Ratio (Random, 95% CI)	0.82 [0.63, 1.05]
1.1 High volume disease	2		Hazard Ratio (Random, 95% CI)	0.67 [0.56, 0.82]
1.2 Low volume disease	2		Hazard Ratio (Random, 95% CI)	1.03 [0.77, 1.38]
2 Grade III to V adverse events	1	375	Risk Ratio (M-H, Random, 95% CI)	2.95 [2.18, 4.00]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 High volume disease	1	181	Risk Ratio (M-H, Random, 95% CI)	2.72 [1.81, 4.07]
2.2 Low volume disease	1	194	Risk Ratio (M-H, Random, 95% CI)	3.29 [2.07, 5.24]
3 Prostate cancer-specific death	1	385	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.72, 1.01]
3.1 High volume disease	1	183	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
3.2 Low volume disease	1	202	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.54, 1.16]
4 Time to progression	2		Hazard Ratio (Random, 95% CI)	0.64 [0.56, 0.73]
4.1 High volume disease	2		Hazard Ratio (Random, 95% CI)	0.58 [0.49, 0.69]
4.2 Low volume disease	2		Hazard Ratio (Random, 95% CI)	0.73 [0.60, 0.91]
5 Discontinuation due to adverse events	1	385	Risk Ratio (M-H, Random, 95% CI)	40.16 [5.58, 289.25]
5.1 High volume disease	1	183	Risk Ratio (M-H, Random, 95% CI)	38.58 [2.36, 629.57]
5.2 Low volume disease	1	202	Risk Ratio (M-H, Random, 95% CI)	41.81 [2.56, 682.07]
6 All adverse events	1	375	Risk Ratio (M-H, Random, 95% CI)	1.11 [1.05, 1.16]
6.1 High volume disease	1	181	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.05, 1.24]
6.2 Low volume disease	1	194	Risk Ratio (M-H, Random, 95% CI)	1.09 [1.02, 1.16]
7 Quality of life	1	544	Mean Difference (IV, Random, 95% CI)	2.88 [-0.68, 6.44]
7.1 High volume disease	1	319	Mean Difference (IV, Random, 95% CI)	4.30 [-0.42, 9.02]
7.2 Low volume disease	1	225	Mean Difference (IV, Random, 95% CI)	1.0 [-4.42, 6.42]

Analysis 2.1. Comparison 2 Volume of Metastases Subgroup, Outcome 1 Time to death due to any cause.

Study or subgroup	Taxane Chemotherapy + ADT N	ADT only N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
2.1.1 High volume disease						
Gravis 2013	0	0	-0.3 (0.171)		25.34%	0.78[0.56,1.09]
Sweeney 2015	0	0	-0.5 (0.117)		33.08%	0.63[0.5,0.79]
Subtotal (95% CI)					58.42%	0.67[0.56,0.82]
Heterogeneity: Tau ² =0; Chi ² =1.03, df=1(P=0.31); I ² =2.91%						
Test for overall effect: Z=4.01(P<0.0001)						
				0.01 0.1 1 10 100	Taxane Chemotherapy + ADT ADT only

Analysis 2.2. Comparison 2 Volume of Metastases Subgroup, Outcome 2 Grade III to V adverse events.

Analysis 2.3. Comparison 2 Volume of Metastases Subgroup, Outcome 3 Prostate cancer-specific death.

Analysis 2.4. Comparison 2 Volume of Metastases Subgroup, Outcome 4 Time to progression.

Analysis 2.5. Comparison 2 Volume of Metastases Subgroup, Outcome 5 Discontinuation due to adverse events.

Analysis 2.6. Comparison 2 Volume of Metastases Subgroup, Outcome 6 All adverse events.

Analysis 2.7. Comparison 2 Volume of Metastases Subgroup, Outcome 7 Quality of life.

Comparison 3. Type of Metastases Subgroup

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to death due to any cause	1		Hazard Ratio (Random, 95% CI)	0.84 [0.65, 1.09]
1.1 Nodal metastases only	1		Hazard Ratio (Random, 95% CI)	1.04 [0.40, 2.69]
1.2 Visceral, bone and/or nodal metastases	1		Hazard Ratio (Random, 95% CI)	0.82 [0.63, 1.08]
2 Grade III to V adverse events	1	375	Risk Ratio (M-H, Random, 95% CI)	3.56 [1.56, 8.17]
2.1 Nodal metastases only	1	61	Risk Ratio (M-H, Random, 95% CI)	6.54 [2.16, 19.85]
2.2 Visceral, bone and/or nodal metastases	1	314	Risk Ratio (M-H, Random, 95% CI)	2.67 [1.95, 3.67]
3 Prostate cancer-specific death	1	385	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.70, 1.02]
3.1 Nodal metastases only	1	63	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.38, 1.82]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Visceral, bone and/or nodal metastases	1	322	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.70, 1.03]
4 Time to progression	1		Hazard Ratio (Random, 95% CI)	0.67 [0.53, 0.84]
4.1 Nodal metastases only	1		Hazard Ratio (Random, 95% CI)	0.84 [0.42, 1.66]
4.2 Visceral, bone and/or nodal metastases	1		Hazard Ratio (Random, 95% CI)	0.65 [0.51, 0.83]
5 Discontinuation due to adverse events	1	385	Risk Ratio (M-H, Random, 95% CI)	28.62 [3.90, 209.89]
5.1 Nodal metastases only	1	63	Risk Ratio (M-H, Random, 95% CI)	11.34 [0.65, 196.88]
5.2 Visceral, bone and/or nodal metastases	1	322	Risk Ratio (M-H, Random, 95% CI)	69.00 [4.27, 1115.90]
6 All adverse events	1	375	Risk Ratio (M-H, Random, 95% CI)	1.11 [1.06, 1.17]
6.1 Nodal metastases only	1	61	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.97, 1.26]
6.2 Visceral, bone and/or nodal metastases	1	314	Risk Ratio (M-H, Random, 95% CI)	1.11 [1.06, 1.18]

Analysis 3.1. Comparison 3 Type of Metastases Subgroup, Outcome 1 Time to death due to any cause.

Study or subgroup	Taxane Chemother- apy + ADT	ADT only	log[Hazard Ratio] (SE)	Hazard Ratio	Weight	Hazard Ratio
	N	N		IV, Random, 95% CI		IV, Random, 95% CI

Test for subgroup differences: $\chi^2=0.21$, $df=1$ ($P=0.64$), $I^2=0\%$

Taxane Chemotherapy + ADT 0.01 0.1 1 10 100 ADT only

Analysis 3.2. Comparison 3 Type of Metastases Subgroup, Outcome 2 Grade III to V adverse events.

Study or subgroup	Taxane Chemother- apy + ADT	ADT only	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI

3.2.1 Nodal metastases only

Gravis 2013 19/30 3/31 6.54[2.16,19.85] 32.1%

Subtotal (95% CI) 30 31 **6.54[2.16,19.85]** 32.1%

Total events: 19 (Taxane Chemotherapy + ADT), 3 (ADT only)

Heterogeneity: Not applicable

Test for overall effect: $Z=3.32$ ($P=0$)

3.2.2 Visceral, bone and/or nodal metastases

Gravis 2013 96/159 35/155 2.67[1.95,3.67] 67.9%

Subtotal (95% CI) 159 155 **2.67[1.95,3.67]** 67.9%

Total events: 96 (Taxane Chemotherapy + ADT), 35 (ADT only)

Heterogeneity: Not applicable

Test for overall effect: $Z=6.07$ ($P<0.0001$)

Total (95% CI) 189 186 **3.56[1.56,8.17]** 100%

Total events: 115 (Taxane Chemotherapy + ADT), 38 (ADT only)

Heterogeneity: $\tau^2=0.24$; $\chi^2=2.37$, $df=1$ ($P=0.12$); $I^2=57.81\%$

Test for overall effect: $Z=3$ ($P=0$)

Test for subgroup differences: $\chi^2=2.31$, $df=1$ ($P=0.13$), $I^2=56.74\%$

Taxane Chemotherapy + ADT 0.01 0.1 1 10 100 ADT only

Analysis 3.3. Comparison 3 Type of Metastases Subgroup, Outcome 3 Prostate cancer-specific death.

Study or subgroup	Taxane Chemother- apy + ADT	ADT only	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI

3.3.1 Nodal metastases only

Gravis 2013 8/31 10/32 0.83[0.38,1.82] 5.74%

Subtotal (95% CI) 31 32 **0.83[0.38,1.82]** 5.74%

Total events: 8 (Taxane Chemotherapy + ADT), 10 (ADT only)

Heterogeneity: $\tau^2=0$; $\chi^2=0$, $df=0$ ($P<0.0001$); $I^2=100\%$

Test for overall effect: $Z=0.48$ ($P=0.63$)

3.3.2 Visceral, bone and/or nodal metastases

Gravis 2013 83/161 98/161 0.85[0.7,1.03] 94.26%

Subtotal (95% CI) 161 161 **0.85[0.7,1.03]** 94.26%

Taxane Chemotherapy + ADT 0.01 0.1 1 10 100 ADT only

Analysis 3.4. Comparison 3 Type of Metastases Subgroup, Outcome 4 Time to progression.

Analysis 3.5. Comparison 3 Type of Metastases Subgroup, Outcome 5 Discontinuation due to adverse events.

Analysis 3.6. Comparison 3 Type of Metastases Subgroup, Outcome 6 All adverse events.

ADDITIONAL TABLES

Table 1. Description of interventions

	Intervention(s) [route, frequency, total dose/day]	Comparator(s) [route, frequency, total dose/day]
GETUG_AFU15, Gravis 2013	I1: docetaxel (75 mg per square meter every 3 weeks for 9 cycles) + ADT ¹	C1: ADT only
CHAARTED, Sweeney 2015	I1: docetaxel (75 mg per square meter every 3 weeks for 6 cycles) + ADT ¹	C1: ADT only
STAMPEDE, James 2016	I1: docetaxel (75 mg per square meter every 3 weeks for 6 cycles) + ADT ¹ I2: docetaxel (75 mg per square meter every 3 weeks for 6 cycles) + Zoledronic Acid (4 mg for six 3-weekly cycles then every 4 weeks for two years) + ADT ¹	C1: ADT only

- denotes not reported

ADT: androgen deprivation therapy

^a The term 'clinical practice setting' refers to the specification of the intervention/comparator as used in the course of a standard medical treatment (such as dose, dose escalation, dosing scheme, provision of contraindications and other important features)

C: comparator; **I:** intervention; **N/CPS:** no specification of clinical practice setting possible

¹ The following therapies were classified as ADT: LHRH agonists or antagonists, bilateral orchidectomy, combined androgen blockade.

Table 2. Baseline characteristics

TABLE 27 Baseline characteristics												
	Intervention(s) and comparator(s)	Duration of follow-up	Number of participants	Description of participants	Trial period [year to year]	Country	Setting	Ethnic groups [%] ¹	Prior local therapy [%] ²	Adjuvant ADT [%]	Gleason 8-10 [%]	High volume of metastasis [%]
GETUG-AFU15 Gravis 2013	I1: docetaxel (75 mg per square meter every 3 weeks for 9 cycles) + ADT ³	4 years	192	Men with metastatic prostate cancer	2004-2008	France	Outpatient	-	32	-	55	48
	C1: ADT ³ only		193					-	24	-	59	47
CHAART-ED, Sweeney 2015	I1: docetaxel (75 mg per square meter every 3 weeks for 6 cycles) + ADT ³	10 years	397	Men with metastatic prostate cancer	2006-2012	USA	Outpatient	10.8	27.2	4.5	60.7	66.2
	C1: ADT ³ only		393					10.9	27.0	4.1	61.8	63.6
STAMPEDE, James 2016	I1: docetaxel (75 mg per square meter every 3 weeks for 6 cycles) + ADT ³	Until death of all randomized patients	592 (362 with metastatic disease)	Men with high-risk locally advanced and metastatic prostate cancer	2005-2013	UK	Outpatient	-	4.1	- for metastatic subgroup	- for metastatic subgroup	- for metastatic subgroup
	C1: ADT ³ only		1,184 (724 with metastatic disease)					-	4.7	- for metastatic subgroup	- for metastatic subgroup	- for metastatic subgroup
- denotes not reported												
ADT: androgen deprivation therapy												
C: comparator; I: intervention; SD: standard deviation												

¹ Ethnic groups included Black and other ethnicities

² Prostatectomy or primary radiation therapy was classified as prior local therapy

³ The following therapies were classified as ADT: LHRH agonists or antagonists, bilateral orchidectomy, combined androgen blockade

APPENDICES

Appendix 1. Search Strategy

(((((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab])) NOT (animals[mh] NOT humans[mh]))) AND (((((((prostatic neoplasms[mh] OR prostatic neoplasms[tw])) OR (prostatic intraepithelial neoplasia[mh] OR prostatic intraepithelial neoplasia[tw])) OR (((cancer* OR carcinoma* OR malignan* OR tumor* OR tumour* OR neopla* AND intraepithelial OR adeno*)) AND prostat*))) AND metastatic)) AND (diterpenes OR paclitaxel OR docetaxel OR cabazitaxel OR taxoids))

PubMed

1. prostatic neoplasms[mh] OR prostatic neoplasms[tw]
2. prostatic intraepithelial neoplasia [mh] OR prostatic intraepithelial neoplasia[tw]
3. cancer* OR carcinoma* OR malignan* OR tumor* OR tumour* OR neopla*
4. 1 OR 2 OR 3
5. intraepithelial OR adeno*
6. 4 AND 5
7. prostat* AND metastatic
8. 6 AND 7
9. diterpenes OR paclitaxel OR docetaxel OR cabazitaxel OR taxoids
10. 8 AND 9
11. randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]
12. 10 AND 11
13. animals
14. humans
15. 12 NOT 13
16. 15 NOT 14

CONTRIBUTIONS OF AUTHORS

NS conceived the review and study design, drafted the protocol, searched for trials, performed study selection, extracted data, assessed risk of bias, performed data analysis, interpreted data, and drafted the review.

YP conceived the review and study design, drafted the protocol, performed study selection, extracted data, assessed risk of bias, performed data analysis, interpreted data, and drafted the review.

GK drafted the protocol, created search strategies, and searched for trials.

BK drafted the protocol, provided clinical and methodological advice on the review, critically revised the review and provided final approval.

SG provided clinical and methodological advice on the review, critically revised the review and provided final approval.

AL drafted the protocol, provided clinical and methodological advice on the review, critically revised the review and provided final approval.

PD conceived the review and study design, drafted the protocol, assessed risk of bias, performed data analysis, interpreted data, and drafted the review.

DECLARATIONS OF INTEREST

NS: none known.

YP: none known.

GK: none known.

BK: none known.

AL: none known.

PD: none known.

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Internal sources

- University of Minnesota Department of Urology, USA.

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External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review is based on a published protocol ([Sathianathan 2017](#)), with differences as described here. We intended to analyze prostate cancer-specific survival as a time-to-event outcome however these data were only available in two trials ([Gravis 2013](#); [James 2016](#)), so it was instead decided to evaluate this as a dichotomous outcome where data were available in all three included trials. In future updates, if data become available, we will endeavour to analyze this outcome as a time-to-event outcome as initially planned. Additionally, we did not include data from the docetaxel + zoledronic acid + ADT arm of the STAMPEDE trial ([James 2016](#)), because there was insufficient data to avoid double-counting the control group, which was the same reference group for the docetaxel + ADT arm of the trial. Furthermore, we renamed the outcome 'serious adverse events' to 'grade III to V adverse events' for clarity as the former has its own, separate definition in the context of clinical trials that is not the same as the definition pre-specified in our protocol.

We were also unable to assess publication bias due to an insufficient number of trials, but in the future if we include 10 studies or more investigating a particular outcome, we will use funnel plots to assess small-study effects. Several explanations can be offered for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials) and publication bias. Therefore, we will interpret results carefully.

NOTES

We have based parts of the [Methods](#) section on a standard template developed by the Cochrane Metabolic and Endocrine Disorders Group, which has been modified and adapted for use by the Cochrane Urology Group.

INDEX TERMS

Medical Subject Headings (MeSH)

Androgen Antagonists [*therapeutic use]; Antineoplastic Agents, Hormonal [adverse effects] [*therapeutic use]; Disease Progression; Prostatic Neoplasms [*drug therapy] [mortality] [pathology]; Quality of Life; Randomized Controlled Trials as Topic; Taxoids [adverse effects] [*therapeutic use]; Withholding Treatment [statistics & numerical data]

MeSH check words

Humans; Male