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Abiraterone acetate in combination with androgen deprivation therapy compared to androgen deprivation therapy only for metastatic hormone-sensitive prostate cancer (Review)

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[Intervention Review]

Abiraterone acetate in combination with androgen deprivation therapy compared to androgen deprivation therapy only for metastatic hormone-sensitive prostate cancer

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ABSTRACT

Background

Systemic androgen deprivation therapy (ADT), also referred to as hormone therapy, has long been the primary treatment for metastatic prostate cancer. Additional agents have been reserved for the castrate-resistant disease stage when ADT start becoming less effective. Abiraterone is an agent with an established role in that disease stage, which has only recently been evaluated in the hormone-sensitive setting.

Objectives

To assess the effects of early abiraterone acetate, in combination with systemic ADT, for newly diagnosed metastatic hormone-sensitive prostate cancer.

Search methods

We searched CENTRAL, MEDLINE, Embase, six other databases, two trials registries, grey literature, and conference proceedings, up to 15 May 2020. We applied no restrictions on publication language or status.

Selection criteria

We included randomized trials, in which men diagnosed with hormone-sensitive prostate cancer were administered abiraterone acetate and prednisolone with ADT or ADT alone.

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 two randomized controlled trials (RCT), with 2201 men, who were assigned to receive either abiraterone acetate 1000 mg once daily and low dose prednisone (5mg) in addition to ADT, or ADT alone. In the LATITUDE trial, the median age and range of men in

the intervention group was 68 (38 to 89) years, and 67 (33 to 92) years in the control group. Nearly all of the men in this study (97.6%) had prostate cancer with a Gleason score of at least 8 (ISUP grade group 4).

Primary outcomes

The addition of abiraterone acetate to ADT reduces the probability of death from any cause compared to ADT alone (hazard ratio [HR] 0.64, 95% confidence interval [CI] 0.56 to 0.73; 2 RCTs, 2201 men; high certainty of evidence); this corresponds to 163 fewer deaths per 1000 men with hormone-sensitive metastatic prostate cancer (210 fewer to 115 fewer) at five years.

Abiraterone acetate in addition to ADT probably results in little to no difference in quality of life compared to ADT alone, measured with the Functional Assessment of Cancer Therapy-prostate total score (FACT-P; range 0 to 156; higher values indicates better quality of life), at 12 months (mean difference [MD] 2.90 points, 95% CI 0.11 to 5.60; 1 RCT, 838 men; moderate certainty of evidence).

Secondary outcomes

Abiraterone plus ADT increases the risk of grades III to V adverse events compared to ADT alone (risk ratio [RR] 1.34, 95% CI 1.22 to 1.47; 1 RCT, 1199 men; high certainty of evidence); this corresponds to 162 more grade III to V events per 1000 men with hormone-sensitive metastatic prostate cancer (105 more to 224 more) at a median follow-up of 30 months.

Abiraterone acetate in addition to ADT probably reduces the probability of death due to prostate cancer compared to ADT alone (HR 0.58, 95% CI 0.50 to 0.68; 2 RCTs, 2201 men; moderate certainty of evidence). This corresponds to 120 fewer death from prostate cancer per 1000 men with hormone-sensitive metastatic prostate cancer (95% CI 145 fewer to 90 fewer) after a median follow-up of 30 months.

The addition of abiraterone acetate to ADT probably decreases the probability of disease progression compared to ADT alone (HR 0.35, 95%CI 0.26 to 0.49; 2 RCTs, 2097 men; moderate certainty of evidence). This corresponds to 369 fewer incidences of disease progression per 1000 men with hormone-sensitive metastatic prostate cancer (456 fewer to 256 fewer) after a median follow-up of 30 months.

The addition of abiraterone acetate to ADT probably increases the risk of discontinuing treatment due to adverse events compared to ADT alone (RR 1.50, 95% CI 1.17 to 1.92; 1 RCT, 1199 men; moderate certainty of evidence). This corresponds to 51 more men (95% CI 17 more to 93 more) discontinuing treatment because of adverse events per 1000 men treated with abiraterone acetate and ADT compared to ADT alone after a median follow-up of 30 months.

Authors' conclusions

The addition of abiraterone acetate to androgen deprivation therapy improves overall survival but probably not quality of life. It probably also extends disease-specific survival, and delays disease progression compared to androgen deprivation therapy alone. However, the risk of grades III to V adverse events is increased, and probably, so is the risk of discontinuing treatment due to adverse events.

PLAIN LANGUAGE SUMMARY

Adding abiraterone acetate to androgen deprivation therapy for the treatment of metastatic hormone-sensitive prostate cancer

Review question

The aim of this review was to find out what the effect of adding abiraterone was, in men with prostate cancer, who were receiving and still responding to hormone therapy.

Background

Abiraterone acetate is a medication that blocks the effect of male sex hormones, and thereby, slows down prostate cancer growth.

More than 15% of men diagnosed with prostate cancer present with disease that has spread beyond the prostate. Another 15% to 30% of men who undergo primary treatment will experience a return of their cancer. Hormone therapy (drugs to reduce the level of male hormones) has been the main treatment for advanced disease, but this does not work forever. Recent studies have looked at whether drugs that block the growth of prostate cancer cells, such as abiraterone acetate, can improve how men do.

Study characteristics

We found two studies (specifically, studies in which 'chance' decided what treatment men got), with a total of 2201 men. The studies compared abiraterone acetate and hormone therapy to hormone therapy alone. In one of the studies, most of the included men had high risk prostate cancer, and had previously undergone local treatment. In the other study, most men had not had previous treatment to their prostate. The evidence is current to 15 May 2020.

Key results

Adding abiraterone acetate to hormone therapy improves overall survival but probably not quality of life. It probably improves cancer-specific survival and reduces disease progression. However, there is also an increase in severe and life-threatening side effects, likely leading to discontinued treatment, with the addition of abiraterone acetate.

Quality of the evidence

We judged the certainty of the evidence to be high for overall survival (time to death from any cause), and severe and life-threatening side effects. This means that our estimates are likely to be close to the actual effect for these outcomes. The certainty of the evidence was moderate for quality of life, cancer-specific survival (time to death from prostate cancer), time to disease progression, and discontinued treatment due to adverse events. This means that our estimates are likely to be close to the actual effect, but there were some limitations in the studies that reduced our confidence in the results.

SUMMARY OF FINDINGS

Summary of findings 1. Abiraterone + ADT versus ADT alone in metastatic, hormone-sensitive prostate cancer

Abiraterone + ADT versus ADT alone in metastatic, hormone-sensitive prostate cancer

Patient or population: men with metastatic, hormone-sensitive prostate cancer
Setting: outpatient; multinational sites across UK, Europe, the Asia–Pacific region, Latin America, and Canada
Intervention: abiraterone + androgen deprivation therapy (ADT)
Comparison: ADT alone

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with ADT only	Risk with abiraterone + ADT
Time to death from any cause	2201 (2 RCTs)	⊕⊕⊕⊕ High	HR 0.64 (0.56 to 0.73)	General population[a]	
				702 per 1000	163 fewer per 1000 (210 fewer to 115 fewer)
Quality of life *(Functional Assessment of Cancer Therapy-prostate [FACT-P; range 0 to 156; higher values = better quality of life])* *measured at 12 months*	838 (1 RCT)	⊕⊕⊕⊖ Moderate[b]		The mean quality of life for men on ADT only was 116 points	The MD for men on abiraterone + ADT was 2.9 points higher (0.11 higher to 5.69 higher)
Grades III to V adverse events *(severe and life threatening, as per the Common Toxicity Criteria v3.0;)* *measured at a median follow-up of 30 months*	1199 (1 RCT)	⊕⊕⊕⊕ High	RR 1.34 (1.22 to 1.47)	Study population[c]	
				477 per 1000	162 more per 1000 (105 more to 224 more)
Time to death due to prostate cancer *measured at a median follow-up of 30.4 months*	2201 (2 RCTs)	⊕⊕⊕⊖ Moderate[d]	HR 0.58 (0.50 to 0.68)	Study population[c]	
				322 per 1000	120 fewer per 1000 (145 fewer to 90 fewer)
Time to disease progression *measured at a median follow-up of 30 months*	2097 (2 RCTs)	⊕⊕⊕⊖ Moderate[d]	HR 0.35 (0.26 to 0.49)	Study population[e]	
				785 per 1000	369 fewer per 1000 (456 fewer to 256 fewer)

Discontinued treatment due to adverse events *measured at a median follow-up of 30 months*	1199 (1 RCT)	⊕⊕⊕⊖ Moderate[d]	RR 1.50 (1.17 to 1.92)	Study population[c]	
				101 per 1000	51 more per 1000 (17 more to 93 more)

*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; **RR:** risk ratio; **HR**: hazard 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

[a]Population data from SEER registry, prostate cancer stage IV 5-year survival (70.2%) in the pre-docetaxel era (2007 to 2013)
[b]Certainty of evidence graded down by one level due to concerns regarding study limitations related to attrition bias
[c]Baseline risk for grades III to V adverse events, prostate cancer-specific death, and discontinued treatment due to adverse events calculated from the control arm of the LATITUDE trial at a median of 30 months follow-up (Fizazi 2017)
[d]Certainty of evidence downgraded by one level due to study limitations
[e]Baseline progression risk calculated from control arm of STAMPEDE trial at 3 years (James 2017)

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 every year (Torre 2015). In the USA, prostate cancer accounts for one in five new diagnoses of all cancers, and is the second leading cause of cancer death amongst men (Siegel 2018). Most prostate cancers tend to be localized at the time of diagnosis, and are managed with active monitoring and surveillance, radical surgery, or radiation therapy (Hamdy 2016). A subgroup of these men experience local or distant disease recurrence after local therapy. The estimated eight-year risk of metastases following radical prostatectomy is 3%, and following external beam radiation therapy is 7% (Zelefsky 2010). Approximately 16% of men present with regional or distant-stage disease at the time of initial diagnosis (Siegel 2018). Therefore, the burden of advanced prostate cancer is considerable.

Since Huggins and colleagues discovered 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 are 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 16 to 30 months (Tannock 2004; Beer 2014; Ryan 2015). Castration-resistant disease is also associated with considerable morbidity and a negative impact on quality of life. It has been reported that 45% of men experienced bone pain at the time of diagnosis, and 80% of men experienced bone pain at a mean follow-up of 18 months (Inoue 2009). Increased incidence of major skeletal events, such as vertebral collapse, fractures, and spinal cord compression, also occur with disease progression (Berruti 2005).

The landscape of 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 randomised trials, examining 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 received docetaxel (Petrylak 2004; Tannock 2004). Since the US Food and Drug Administration approval for the use of docetaxel in metastatic disease, a number of other agents have entered the market, such as abiraterone acetate (de Bono 2011; Ryan 2015), enzalutamide (Scher 2012; Beer 2014), cabazitaxel (de Bono 2010), and the therapeutic vaccine sipuleucel-T (Kantoff 2010). The seminal findings with docetaxel laid the foundation to revisit the concept of upfront chemohormonal therapy, using these newer agents to potentially delay the progression of androgen-dependent disease to its lethal castration-resistant form. The newer drugs all focused on men with castration-resistant prostate cancer. Following the publication of randomised trials demonstrating a survival benefit, docetaxel was introduced earlier in the disease stage, concomitantly with systemic androgen ablation (Sweeney 2015; James 2016). As a result, there has been ongoing interest in using other agents that are currently used in the castration-resistant setting at an earlier stage of the disease course, such as abiraterone acetate.

Description of the intervention

Abiraterone acetate is an androstane derivative that blocks the activity of the enzyme 17alpha-monooxygenase (17alpha-hydrolase/C17,20 lyase complex). It is currently approved for use in metastatic castration-resistant prostate cancer. It is administered orally, at a dose of 1000 mg daily in combination with prednisone 5 mg.

Abiraterone acetate is a pro-drug that is almost completely converted to abiraterone — the active metabolite — in the liver. It has a mean terminal half-life of 24 hours, and reaches maximal plasma concentration at a median two hours after administration. In plasma, abiraterone is highly bound to both albumin and a1-glycoprotein. The drug is metabolized through several hepatic pathways, therefore, hepatic impairment decreases the elimination of abiraterone. It is recommended that the dose of abiraterone is reduced to 250 mg daily for people with moderate hepatic impairment, and is contraindicated in those with severe hepatic impairment. Abiraterone is a substrate of CYP3A4 and SULT2A1, thus, its elimination is effected by other agents that are involved in these pathways, including rifampicin and ketoconazole.

Adverse effects of the intervention

Abiraterone is a generally well-tolerated drug with no dose-limiting toxicities observed in phase I trials (Attard 2008). Most adverse effects are mild to moderate (grades I to II) in nature, and include fatigue, back pain, nausea, constipation, bone pain, hot flashes, diarrhea, and arthralgia (Ryan 2013). Abiraterone treatment results in a mineralocorticoid excess that can lead to hypertension, hypokalemia, and fluid retention. However, the incidence of these side effects was only 4% for men with grade III, 2% for men with grade IV, and less than 1% in men with chemotherapy-naïve castration-resistant prostate cancer (Ryan 2013). Prednisone is commonly prescribed concomitantly to mitigate these side effects. It was observed that abiraterone acetate treatment led to abnormalities of liver function tests in approximately 11% of men, but these were severe in only 4% (Fizazi 2012; Ryan 2013). There was no statistically significant increase in cardiac events with abiraterone treatment compared to placebo in phase III trials in men with castration-resistant prostate cancer. It should be noted that the aforementioned toxicity data are derived from men with castration-resistant prostate cancer who are different to the population included in this review, and hence the absolute rates may differ.

How the intervention might work

Abiraterone acetate is a selective irreversible inhibitor of CYP17A (17α-hydroxylase/17,20-lyase), which is a cytochrome P450 enzyme

that is important in the biosynthesis of androgen. CYP17A is expressed in the adrenal glands, and is involved in the production of adrenal androgens, and facilitates de novo synthesis of androgens by prostate cancer cells. Abiraterone has been demonstrated to directly inhibit androgen receptor activity, including the androgen receptor itself (Soifer 2012). Because prostate cancer cell growth and survival is largely androgen-dependent, abiraterone acetate has the potential to delay or inhibit cancer progression by decreasing the production of androgens and blocking androgen receptor activity (Heinlein 2004).

Administering abiraterone acetate during the early stages of metastatic prostate cancer, rather than waiting for the disease to progress, could be beneficial. Delaying the development of castration-resistant prostate cancer has important implications. Men are able to maximize their quality of life by delaying the morbidity associated with castration-resistant disease and the need for further treatment, which has potential adverse events. Since they typically are healthier during the early stages of metastatic prostate cancer, they are more able to withstand the toxicities of treatment. The higher disease burden, and overall decline in functional status experienced with the development of castration-resistant prostate cancer, will exclude a sizable proportion of men from even receiving abiraterone acetate at this late stage.

Why it is important to do this review

Following the publication of randomized trials that demonstrated a survival benefit for upfront docetaxel with androgen deprivation therapy in metastatic hormone-sensitive prostate cancer, there has been interest in determining whether other agents used in the castration-resistant setting can be administered earlier in the hormone-sensitive setting (Sweeney 2015; James 2016).

Three systematic reviews have sought to critically appraise the entire body of trial evidence addressing this question. Rydzewska and colleagues omitted certain outcomes important to men with prostate cancer, such as quality of life, and did not use the GRADE approach to appraise the quality of evidence (Rydzewska 2017). Two network meta-analyses had similar shortcomings (Vale 2018; Wallis 2018). Therefore, this Cochrane Review will aim to critically evaluate the evidence in a prescribed manner, and focus on outcomes that are important to men with metastatic hormone-sensitive prostate cancer, using the most methodologically rigorous approach.

OBJECTIVES

To assess the effects of early abiraterone acetate, in combination with androgen deprivation therapy, for newly diagnosed metastatic hormone-sensitive prostate cancer.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised trials, regardless of their publication status or language of publication. We excluded cluster-randomized, cross-over and quasi-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, determined by cross-sectional imaging (computer tomography [CT], magnetic resonance imaging [MRI], positron emission tomography [PET]), with or without bone scans. This included both men who had, and those who had not undergone local therapy. We only included men receiving immediate abiraterone acetate in combination with androgen deprivation therapy for their prostate cancer. Men who started abiraterone acetate within 120 days of beginning androgen deprivation therapy were considered to be receiving 'early' combination therapy. We included men who had previously received adjuvant or neoadjuvant androgen deprivation therapy if their metastases occurred at least 12 months after they stopped hormone therapy. Men receiving concurrent osteoprotective therapy (e.g. bisphosphonates) were 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.

If we identified studies in which only a subset of the men were relevant to this review, we included them if data were available separately for the relevant subset.

Types of interventions

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

Experimental interventions

- Abiraterone acetate and prednisone in combination with androgen deprivation therapy (using methods outlined under 'Comparator interventions' below).

Comparator interventions

- Androgen deprivation therapy alone (using luteinizing hormone-releasing hormone agonist or antagonist; non-steroidal antiandrogen monotherapy; combination of antiandrogen plus luteinizing hormone-releasing hormone agonist [maximum androgen blockade], or bilateral orchiectomy).

Comparisons

- Abiraterone acetate and prednisone in combination with androgen deprivation therapy versus androgen deprivation therapy alone.

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
- Quality of life

Secondary outcomes

- Grades III to V adverse events

- Time to death due to prostate cancer
- Time to disease progression
- Discontinued treatment due to adverse events

Method and timing of outcome measurement

- Time to death due to any cause, was the time from randomization to death from any cause (time-to-event outcome).
- Overall quality of life at 12 months, or as reported; 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 - Prostate Scales (FACT-P; range 0 to 156; higher values indicate better quality of life) questionnaires (continuous outcome).
- Grades III to V adverse events at 12 months, or as reported, according to the Common Toxicity Criteria (CTCAE) v3.0; occurring at any time during treatment; such as sudden death, neutropenia, febrile neutropenia, fatigue, gastrointestinal disorders (including diarrhea, constipation, and vomiting), stomatitis, neuropathy, thromboembolism, thrombocytopenia, or renal impairment (dichotomous outcome).
- Time to death due to prostate cancer, was the time from randomization until death from prostate cancer (time-to-event outcome).
- Time to disease progression, was the time from randomization until clinical, biochemical, or radiographic progression (time-to-event outcome). Biochemical and radiographic progression were defined using the criteria specified by the Prostate Cancer Working Group 2 (Scher 2008). Clinical progression was defined as clinical deterioration due to cancer.
- Discontinued treatment due to adverse events, was the number of men who ceased treatment due to an adverse event caused by the treatment (dichotomous outcome).

When we were unable to retrieve the information needed to analyze time-to-event outcomes, we attempted to assess the number of events per group, for dichotomized outcomes at one, three, and five years after starting abiraterone treatment (Differences between protocol and review).

Main outcomes for 'Summary of findings' table

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

1. Time to death due to any cause
2. Quality of life
3. Grades III to V adverse events
4. Time to death due to prostate cancer
5. Time to disease progression
6. Discontinued treatment due to adverse events

Search methods for identification of studies

We conducted a comprehensive search with no restrictions on the language of publication, or publication status in October 2019. We re-ran searches within six months of anticipated publication of the review to capture any recently published relevant records (15 May 2020).

Electronic searches

We searched the following sources from inception of each database.

- Cochrane Library 2020, issue 4 (searched 15 May 2020; Appendix 1)
  - *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 via Ovid (1946 to 15 May 2020; Appendix 2);
- Embase via Ovid (1947 to 15 May 2020; Appendix 3);
- Scopus (1966 to 15 May 2020; Appendix 4);
- Web of Science (1900 to 15 May 2020; Appendix 5);
- LILACS (Latin American and the Caribbean Health Sciences Literature; 1982 to 15 May 2020; Appendix 6).

We also searched the following.

- ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (ICTRP) search portal (apps.who.int/trialsearch);
- Grey literature repository from the current Grey Literature Report (www.greylit.org).

We did not detect additional relevant key words during any of the electronic or other searches that necessitated modification of the search strategy.

Searching other resources

We attempted to identify other potentially eligible trials or ancillary publications by searching the reference lists of included trials, and identified 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 searched abstract proceedings of relevant meetings, such as the American Urological Association, European Association of Urology, and American Society of Clinical Oncology since the approval of abiraterone acetate (2011 to 2018) for unpublished studies.

Data collection and analysis

Selection of studies

We used reference management software to identify and remove potential duplicate records (EndNote 2016). Two review authors (NS, MO) independently scanned the abstract, title, or both, of the remaining retrieved records, to determine which studies should be assessed further. Two review authors (NS, MO) independently investigated all potentially relevant records as full text, mapped records to studies, and classify studies as included studies, excluded studies, studies awaiting classification, or ongoing studies, in accordance with the criteria provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We resolved any discrepancies through consensus, or recourse to a third review author (FK) if needed. We documented reasons for excluding studies that may have reasonably been expected to be included in the review in a 'Characteristics of excluded studies' table. We present a PRISMA flow diagram showing the process of study selection (Liberati 2009).

Data extraction and management

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

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

- Study design;
- Study dates (if dates are not available then this will be reported as such);
- Study settings and country;
- Participant inclusion and exclusion criteria (e.g. age, disease stage, comorbidities, pretreatment);
- Participant details, baseline demographics (e.g. age, disease stage);
- The number of participants by study arm;
- Details of relevant experimental and comparator interventions, such as dose, route, frequency, and duration;
- Definitions of relevant outcomes, 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 to calculate summary statistics and measures of variance. For dichotomous outcomes, we attempted to obtain numbers of events and totals to populate a 2×2 table, as well as summary statistics with corresponding measures of variance. For continuous outcomes, we attempted to obtain means and standard deviations, or data necessary to calculate this information. For time-to-event outcomes, we attempted to obtain hazard ratios (HRs) with corresponding measures of variance, or data necessary to calculate this information.

We resolved any disagreements by discussion; if required, we consulted with a third review author (FK).

In future, if we identify any, we will provide information, including trial identifier, on potentially relevant ongoing studies in the '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

We maximized yield of information by mapping all publications (duplicate publications, companion documents, or multiple reports of the study) to a unique study ID, and collating all available data. We used the most complete dataset, aggregated across all known publications. If in 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, MO) independently assessed the risk of bias of each included study. We resolved disagreements by consensus, or by consulting with a third review author (FK).

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 presented a 'Risk of bias' summary figure to illustrate these findings.

For selection bias (random sequence generation and allocation concealment), we evaluated risk of bias at a trial level.

For performance bias (blinding of participants and personnel), we considered that all outcomes were similarly susceptible to performance bias.

For detection bias (blinding of outcome assessment), we grouped outcomes as susceptible to detection bias (subjective), or not susceptible to detection bias (objective).

We defined the following as subjective outcomes.

- Serious adverse events;
- Time to death due to prostate cancer;
- Time to disease progression;
- Discontinued treatment due to adverse events;
- Quality of life.

We defined the following as an objective outcome.

- Time to death due to any cause.

We assessed attrition bias (incomplete outcome data) on an outcome-specific basis, and presented the judgement for each outcome separately in the 'Risk of bias' tables.

For reporting bias (selective reporting), we evaluated risk of bias at a trial level.

We further summarized the risk of bias across domains for each outcome in each included study, and 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, unless different studies used different measures to assess the same outcome, in which case we expressed data as standardized mean differences (SMD) with 95% CIs. We expressed time-to-event data as hazard ratios (HRs) with 95% CIs.

Unit of analysis issues

The unit of analysis was the individual man.

Dealing with missing data

We attempted to obtain missing data from study authors, and conducted intention-to-treat (ITT) analyses if data were available; otherwise, we conducted 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), by visually inspecting the forest plots to assess the amount of overlap of CIs, and calculating 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

If 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. We did not use funnel plots to assess for reporting bias because we only included two trials.

Data synthesis

We summarized data using a random-effects model. We interpreted random-effects meta-analyses with due consideration of the whole distribution of effects. In addition, we conducted statistical analyses according to the statistical guidelines outlined 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 2014 software to perform analyses.

Subgroup analysis and investigation of heterogeneity

We expected the following characteristics to be potential effect modifiers, and carried out subgroup analyses to investigate interactions.

- Volume of metastases: high volume, defined according to expert consensus as visceral, four or more bone metastases including one beyond the pelvis and vertebral column, or both, versus low volume (Gillessen 2015)
- Previous local treatment: men who had undergone radical surgery, or radiation therapy, or both, and then developed metastases were separated from those who had not undergone any previous treatment, and instead presented with metastatic disease.

We tested for subgroup differences in Review Manager 2014 to compare subgroup analyses.

Sensitivity analysis

We planned to perform sensitivity analyses on the primary outcomes in order 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. Studies with more than two bias domains assessed as unclear risk, were classified as being at high risk from bias, overall.

Summary of findings and assessment of the certainty of the evidence

We presented the overall quality of the evidence for each outcome according to the GRADE approach, which takes into account five criteria, related to internal validity (risk of bias, inconsistency, imprecision, publication bias), and external validity (directness of results; [Guyatt 2008]). For each comparison, two review authors (NS and MO) independently rated the quality of evidence for each outcome as high, moderate, low, or very low, using GRADEpro GDT. We resolved any discrepancies by consensus, or, if needed, by arbitration by a third review author (FK). 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 the estimate of effect for each outcome (Guyatt 2011; Schünemann 2011). If meta-analysis was not possible, we presented results in a narrative 'Summary of findings' table.

RESULTS

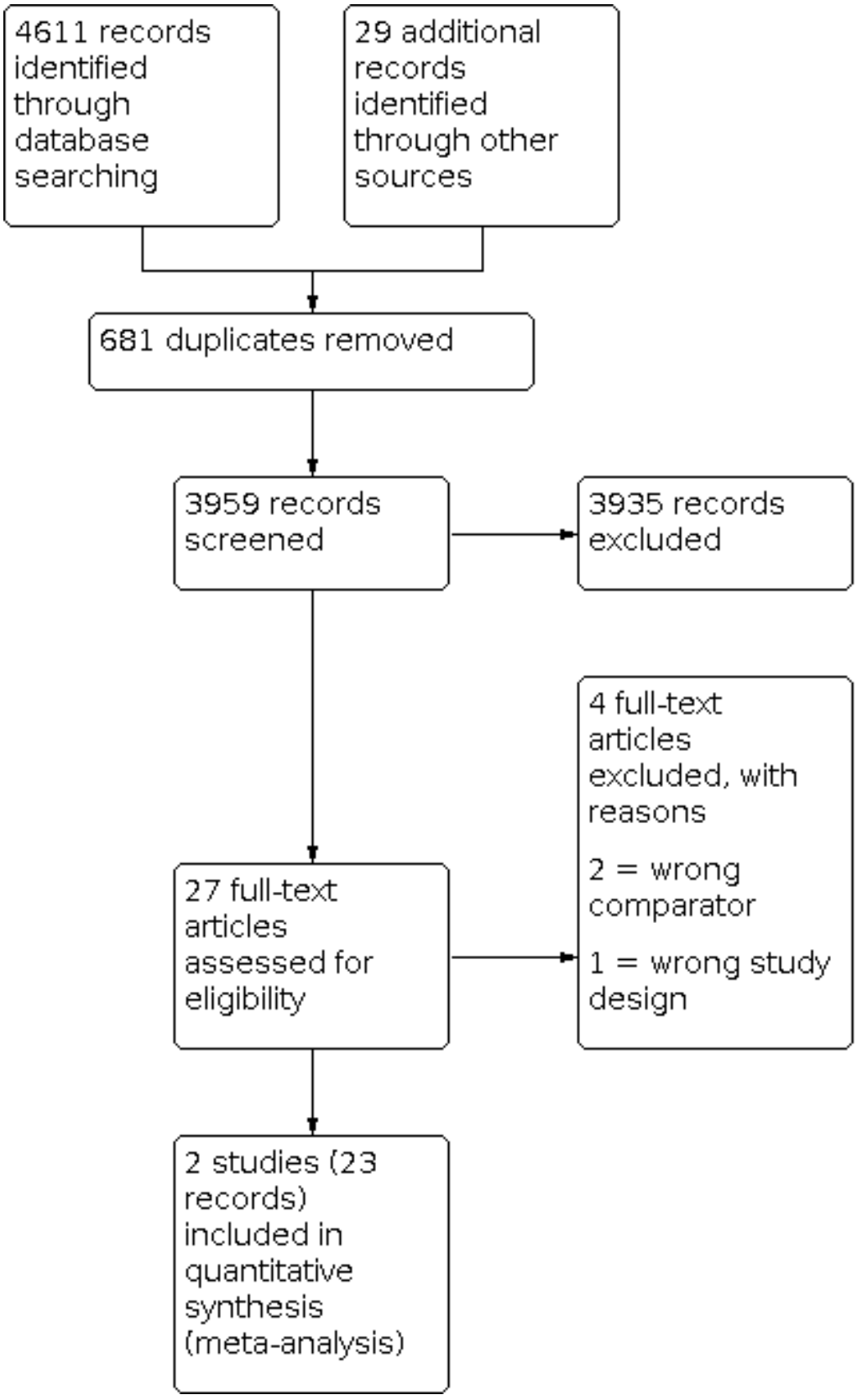
Description of studies

We included two randomized controlled trials (RCT), details of which are presented in the 'Characteristics of included studies' table, Table 1, and Table 2.

Results of the search

We identified 4611 records through database searching up to 15 May 2020. After removing duplicates, we screened the titles and abstracts of 3959 records, 3935 of which we eliminated as not eligible. We reviewed 27 full-text articles, and excluded three trials (four records) that did not meet the inclusion criteria. We included a total of two studies (23 records) in this review. We did not identify any trials that were either ongoing, or completed but not yet published. The flow of literature through the assessment process is shown in the PRISMA flowchart (Figure 1).

Figure 1. Study flow diagram



Included studies

Sources of data

Both included trials were identified through the literature search. There were multiple abstracts and conference proceedings for each of the included trials.

Study design and settings

The included studies were both randomized trials; Fizazi 2017 (LATITUDE trial) was described as a double-blind, placebo-controlled study, whereas James 2017 (STAMPEDE trial) was an open-label study.

Participants

This review included a total of 2201 men with metastatic, hormone-sensitive prostate cancer, 1097 of whom received abiraterone acetate and prednisone in addition to androgen deprivation therapy. One trial also enrolled 915 men with non-metastatic disease, who were not included in this review (James 2017).

The STAMPEDE trial (James 2017) did not report baseline characteristics separately for the subgroup of men with metastatic, hormone-sensitive disease, and therefore, the following data are from the LATITUDE trial (Fizazi 2017) only. The median age and range of the men in the intervention group was 68 years (38 to 89) and 67 years (33 to 92) in the control group. The prostate cancer in nearly all of the men (97.6%) in Fizazi 2017 had a Gleason score of at least 8 (grade IV). A similar proportion of the men also had at least three bony metastases at the time of screening (97.7%). The majority of men in Fizazi 2017 had undergone previous treatment for their prostate cancer (93.4%). In contrast, in the metastatic subgroup in James 2017, nearly all of the men were newly diagnosed with their metastases, and had no previous prostate cancer treatment (93.9%).

The inclusion criteria included men over the age of 18 years, who had histologically or cytologically proven adenocarcinoma of the prostate, and metastatic disease proven by computer tomography (CT) or magnetic resonance imaging (MRI). Histological confirmation was not required in James 2017 if the men had multiple sclerotic bone metastases with a prostate-specific antigen (PSA) ≥100 ng/mL. Men in Fizazi 2017 were required to have two of the following three high-risk prognostic factors: Gleason score ≥ 8, at least three lesions on bone scan, or the presence of visceral metastases.

Men who had undergone previous curative treatment for their metastatic prostate cancer were excluded. However, Fizazi 2017 permitted the men to receive up to three months of pharmacological or surgical castration therapy. James 2017 permitted adjuvant or neoadjuvant hormone treatment, as long as therapy had been completed at least 12 months prior to randomization, and had been no longer than 12 months in duration. Fizazi 2017 excluded men with small cell carcinoma of the prostate, brain metastases, or other active malignancies.

Interventions and comparators

The two included trials administered abiraterone acetate 1000 mg once daily with low-dose prednisone (5 mg) to the men in the active intervention arm until PSA, radiological, or clinical progression of the disease, or until another treatment was started. All of the men were given androgen deprivation therapy (ADT) through either surgical or pharmacological means, at the discretion of the investigator.

Outcomes

Time to death due to any cause was reported in both trials, and we analyzed the data using an intention-to-treat approach. We analyzed quality of life using the Functional Assessment of Cancer Therapy–prostate (FACT-P) score from Fizazi 2017, through additional data provided by the study authors. James 2017 did not report this outcome.

Data for time to death from prostate cancer, and time to disease progression were available in both trials. Only Fizazi 2017 provided the required information for grades III to V adverse events, and discontinued treatment due to adverse events. There were insufficient data in James 2017, because although these outcomes were assessed, the published manuscript reported both non-metastatic and metastatic participants together, and did not stratify the outcome by these subgroups.

We contacted authors of both included studies to obtain additional data. but only received additional data from Fizazi 2017.

Funding

Both trials received funding from Janssen, which developed abiraterone acetate. James 2017 also received funding from other industry and government sources. Conflicts of interests with pharmaceutical companies were reported in all studies.

Excluded studies

We excluded three studies, which are outlined in the 'Characteristics of excluded studies' table. Two studies were excluded because the comparator was docetaxel plus ADT rather than ADT alone (Sydes 2017; Feyerabend 2018); the third was the wrong study design.

Risk of bias in included studies

Detailed results of the 'Risk of Bias' assessment are provided in Figure 2 and Figure 3, 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

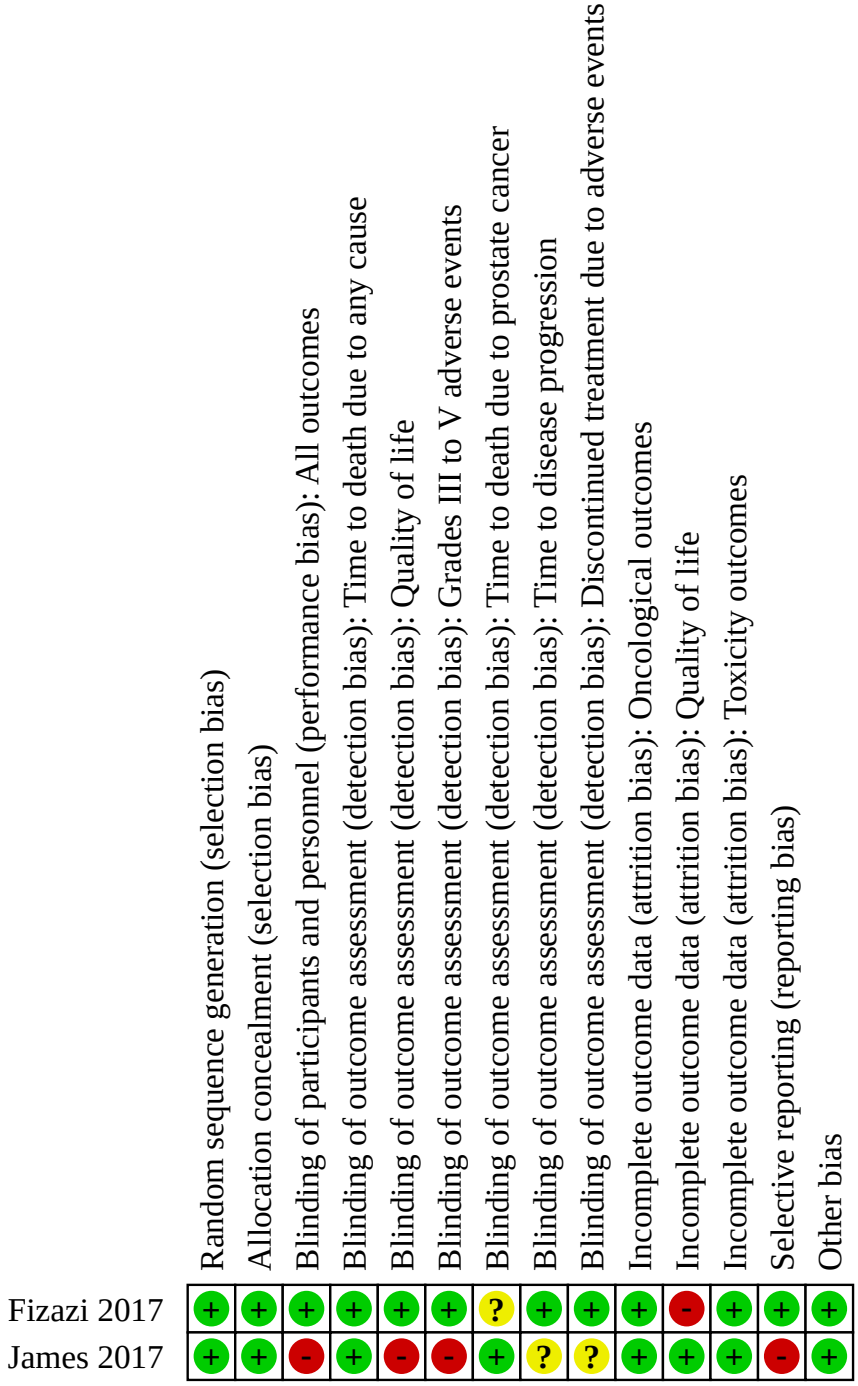
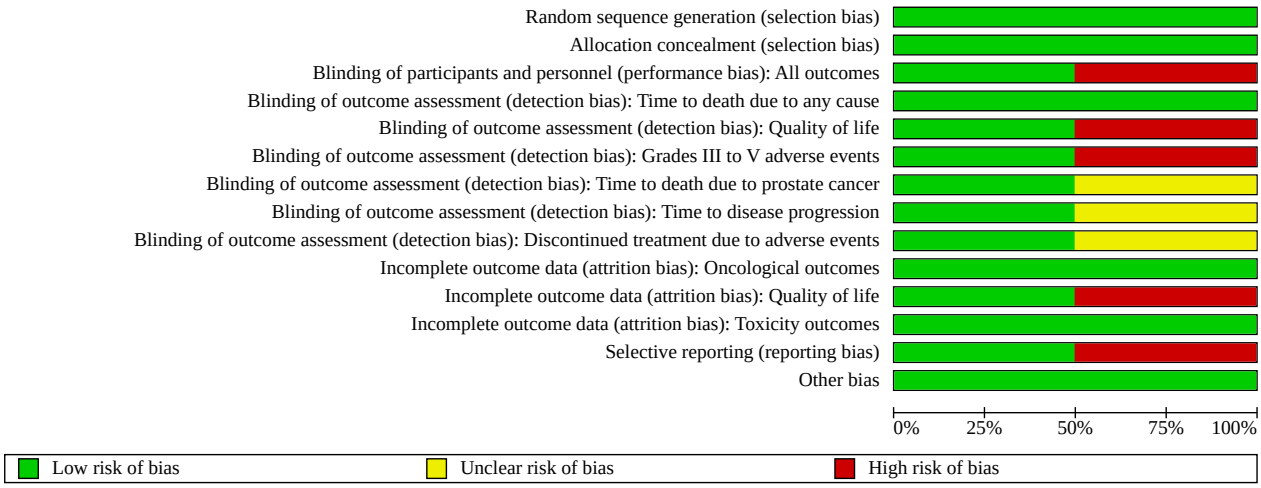


Figure 3. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies.



Allocation

Random sequence generation

We rated both trials at low risk of bias because either computer algorithms were used (James 2017), or the sequence was created centrally, by an independent, uninvolved, third-party (Fizazi 2017).

Allocation concealment

We rated both trials at low risk of bias because allocation was performed centrally.

Blinding

Blinding of participants and personnel

We rated Fizazi 2017 at low risk of performance bias, because we judged that both participants and personnel were appropriately blinded, whereas James 2017 was an open-label trial, and at high risk of performance bias.

Blinding of outcome assessment

- Time to death due to any cause: this is an objective outcome that is unlikely to be affected by blinding, and therefore, we rated both studies at low risk of detection bias.
- Quality of life: this was measured by self-assessment questionnaires that were completed by blinded participants in Fizazi 2017, and therefore, we rated it at low risk of detection bias; participants were not blinded in James 2017, and thus, we rated it at high risk of performance bias.
- Grades III to V adverse events: blinded investigators determined the severity of adverse events in Fizazi 2017, so we rated this at low risk of detection bias. Unblinded investigators rated the severity of adverse events in James 2017, so we rated it at high risk of performance bias.
- Time to death due to prostate cancer: we rated James 2017 at low risk of bias because the cause of death was determined by a blinded reviewer. It was not clear who was responsible for determining the cause of death in Fizazi 2017, or whether they were appropriately blinded, therefore, we rated this as unclear risk of bias.
- Time to disease progression: we rated Fizazi 2017 at low risk of bias, because Individuals who determined progression (using radiology, PSA, or both) were blinded. There was no information in James 2017 regarding the blinded status of the individuals who assessed progression, and thus, we rated this as unclear risk of bias.
- Discontinued treatment due to adverse events: we rated Fizazi 2017 at low risk of bias, because although not clearly specified, the reasons for discontinuing treatment were likely to be reported by investigators who were blinded to treatment allocation. There was no information in James 2017 regarding blinding of the individuals responsible for determining the reasons for discontinued treatment, and therefore, we rated it as unclear risk of bias.

Incomplete outcome data

We grouped outcomes into groups of similar susceptibility to attrition bias: oncological outcomes (time to death due to any cause, time to death due to prostate cancer, time to progression), quality of life, and toxicity outcomes (grades III to V adverse events and discontinuing due to adverse events).

- Oncological outcomes: we rated both studies at low risk of bias, because the men were analyzed in the groups to which they were randomized, in an intention-to-treat manner, and the rates of loss to follow-up were low.
- Quality of life: we rated Fizazi 2017 at high risk of attrition bias, because 70% of the men completed the FACT-P score at 12 months. Quality of life was not reported in James 2017.
- Toxicity outcomes: we rated both studies at low risk bias, because the men were analyzed in the group to which they were randomized, in an intention-to-treat manner, and the rates of loss to follow-up were low.

Selective reporting

We rated Fizazi 2017 at low risk of reporting bias, because they reported all outcomes pre-specified in the protocol. We rated James 2017 at high risk of reporting bias, because quality of life

was stated as a secondary outcome in the protocol, but was not reported.

Other potential sources of bias

We did not find any other sources of bias in the two included studies, and therefore, we other sources of bias at low risk.

Effects of interventions

See: **Summary of findings 1** Abiraterone + ADT versus ADT alone in metastatic, hormone-sensitive prostate cancer

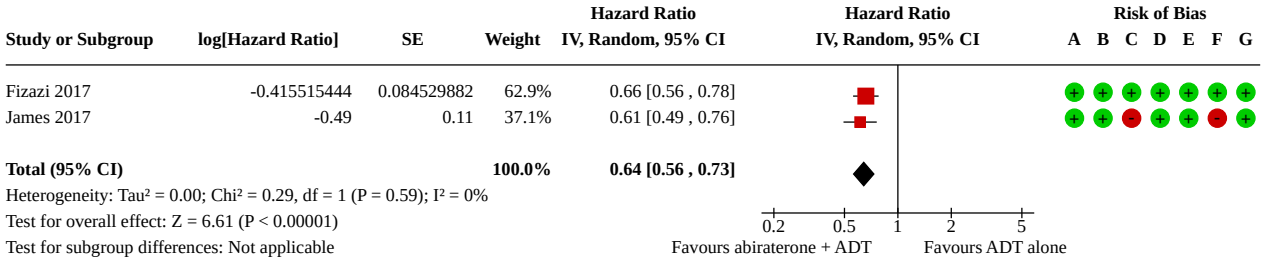
1. Abiraterone acetate and prednisone in combination with androgen deprivation therapy versus androgen deprivation therapy only

1.1 Time to death due to any cause

Two trials measured this outcome (Fizazi 2017; James 2017).

Abiraterone acetate in addition to androgen deprivation therapy (ADT) reduced the probability of dying from any cause more than ADT alone (hazard ratio [HR] 0.64, 95% confidence interval [CI] 0.56 to 0.73; two RCTs, 2201 men; Analysis 1.1; Figure 4; high-certainty evidence). Compared to the five-year survival for stage IV prostate cancer in the Surveillance, Epidemiology, and End Results (SEER) registry in the pre-docetaxel era (2007 to 2013; Rawla 2019), the addition of abiraterone acetate resulted in 163 fewer deaths (95% CI -210 to -115) from all causes per 1000 men with hormone-sensitive metastatic prostate cancer.

Figure 4. Forest plot of comparison: 1 Abiraterone + ADT vs ADT alone, outcome: 1.1 Time to death due to any cause.



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias): Time to death due to any cause
(E) Incomplete outcome data (attrition bias): Oncological outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

1.2 Quality of life

One trial measured quality of life with the FACT-P questionnaire (Fizazi 2017).

Abiraterone acetate in addition to ADT probably results in a small, likely not clinically meaningful improvement in quality of life at 12 months compared to ADT alone (mean difference [MD] 2.90 points, 95% CI 0.11 to 5.60; one RCT, 838 men; Analysis 1.2; moderate-certainty evidence) assuming a minimally clinically important difference of 6 - 10 (Cella 2009). We downgraded the certainty of the evidence due to concerns regarding possible attrition bias.

1.3 Grades III to V adverse events

One trial measured grades III to V severe adverse events (Fizazi 2017).

Abiraterone acetate in addition to ADT increases the risk of grades III to V adverse events compared to ADT alone (risk ratio [RR] 1.34, 95% CI 1.22 to 1.47; one RCT, 1199 men; Analysis 1.3; high-certainty evidence). This corresponds to 162 more (95% CI 105 to 224) grades III to IV adverse events per 1000 men treated with abiraterone acetate and ADT compared to ADT alone, at a median follow-up of 30 months.

1.4 Time to death due to prostate cancer

Two trials measured this outcome (Fizazi 2017; James 2017).

Abiraterone acetate in addition to ADT probably reduces the probability of prostate cancer-specific death compared to ADT alone (HR 0.58, 95% CI 0.50 to 0.68; two RCTs, 2201 men; Analysis 1.4; moderate-certainty evidence). Compared to the event rate in the control arm of the LATITUDE trial at a median follow-up of 30.4 months, the addition of abiraterone acetate resulted in 120 fewer (95% CI -145 to -90) deaths from prostate cancer per 1000 men with hormone-sensitive metastatic prostate cancer (Fizazi 2017). We downgraded the level of the certainty due to concerns regarding possible performance bias.

1.5. Time to disease progression

Two trials measured this outcome (Fizazi 2017, James 2017).

Abiraterone acetate in addition to ADT probably reduces the probability of progression of disease compared to ADT alone (HR 0.35, 95% CI 0.26 to 0.49; two RCTs, 2201 men; Analysis 1.5;

moderate-certainty evidence). Compared to the three-year event rate in the control arm of the STAMPEDE trial, the addition of abiraterone acetate resulted in 369 fewer (95% CI -456 to -256) incidents of disease progression per 1000 men with hormone-sensitive metastatic prostate cancer (James 2017). We downgraded the certainty of the evidence due to concerns regarding possible detection bias.

1.6 Discontinued treatment due to adverse events

One trial measured this event (Fizazi 2017).

Abiraterone acetate in addition to ADT probably increases the risk of discontinuing treatment due to adverse events compared to ADT alone (RR 1.50, 95% CI 1.17 to 1.92; one RCT, 1199 men; Analysis 1.6; moderate-certainty evidence). This corresponds to 51 more men (95% CI 17 to 93) discontinuing treatment because of adverse events per 1000 men treated with abiraterone acetate and ADT compared to ADT alone, at a median follow-up of 30 months. We downgraded the certainty of the evidence due to concerns regarding possible detection bias and imprecision.

2. Subgroup analysis: volume of metastases

2.1 Time to death due to any cause

The probability of dying from any cause for men with low volume of metastases was HR 0.68 (95% CI 0.50 to 0.91); for men with high volume of metastases it was HR 0.61 (95% CI 0.53 to 0.71; Analysis 2.1). The test for interaction was not significant (P = 0.56; I^2 = 0%).

2.2 Quality of life

The mean difference in FACT-P scores for the men with low volume of metastases who received abiraterone acetate was -2.03 (95%CI -10.98 to 6.92); for men with high volume of metastases, the mean difference was 3.68 (95%CI 0.73 to 6.63; Analysis 2.2). The test for interaction was not significant (P = 0.23; I^2 = 29%).

2.3 Grades III to V adverse events

We were unable to obtain the required data to conduct a subgroup analysis for this outcome.

2.4 Time to death due to prostate cancer

The probability of dying from prostate cancer for men with low volume disease was HR 0.67 (95%C CI 0.44 to 1.01); for men with high volume disease it was HR 0.57 (95% CI 0.49 to 0.67; Analysis 2.3). The test for interaction was not significant (P = 0.50; I^2 = 0%).

2.5 Time to progression

The probability of progression of disease for men with low volume of metastases was HR 0.46 (95% CI 0.33 to 0.63); for men with high volume of metastases, the HR was 0.46 (95% CI 0.31 to 0.69; Analysis 2.4). The test for interaction was not significant (P = 0.97; I^2 = 0%).

2.6 Treatment discontinued due to adverse events

We were unable to obtain the required data to conduct a subgroup analysis for this outcome.

3. Subgroup analysis: previous local treatment

We were unable to obtain the required data to conduct a subgroup analysis for this outcome.

4. Sensitivity analysis

For the primary outcome of time to death due to any cause, we rated both trials at overall low risk of bias, therefore, the results of the sensitivity analysis are the same as Analysis 1.1.

For grades III to V adverse events, we only rated Fizazi 2017 at overall low risk of bias, therefore, the results of the sensitivity analysis are the same as Analysis 1.3.

We were unable to conduct a sensitivity analysis for quality of life.

DISCUSSION

Summary of main results

We included two randomized trials with 2201 men (Table 1; Table 2). Compared to androgen deprivation therapy (ADT) alone, the addition of abiraterone acetate to ADT for metastatic hormone-sensitive prostate cancer probably improves overall and progression-free survival. The addition of abiraterone acetate to ADT appears to result in a large reduction in the risk of progression. It also probably reduces the probability of prostate cancer-specific death, and leads to a small, and not clinically meaningful improvement in quality of life. However, the addition of abiraterone acetate to ADT probably increases the risk of grades III to V adverse events, and discontinued treatment from adverse events. The benefit of adding abiraterone acetate to ADT is seen in both low- and high-volume disease.

Overall completeness and applicability of evidence

The majority of included men were newly diagnosed with metastatic prostate cancer, and thus, we are uncertain whether the treatment effect would be the same for those with prior local treatment, although there is currently no evidence to suggest otherwise. We had concerns regarding attrition bias for the quality of life outcome, because only 70% of the men in the LATITUDE study completed the questionnaire at 12 months; therefore, this may not reliably reflect the true treatment effect for this population.

There were insufficient data to conduct all of the intended subgroup analyses, so we are uncertain whether the volume of disease or prior local treatment impacts the effectiveness of abiraterone acetate; the limited data available for some of the outcomes did not show any difference. Post hoc analysis in the STAMPEDE trial did show that overall survival was improved with the addition of abiraterone acetate in men with de novo metastatic disease, regardless of disease volume (James 2017).

Both of the included studies were funded by industry, and study authors had extensive relationships with industry. This should be considered when interpreting and applying the results.

Quality of the evidence

Overall, we rated the certainty of evidence as moderate or high, reflecting the methodological robustness of the trials included in this review, especially the LATITUDE study, which was a double-blind, randomized trial, in which both participants and personnel were appropriately randomized, allocation was concealed, and they were blind to the treatment group (Fizazi 2017). On the other hand, the STAMPEDE trial was an open-label study, and therefore, when data from this trial were included, we downgraded

the evidence by one level due to study limitations, for risk of performance and detection biases (James 2017).

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, 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.

Agreements and disagreements with other studies or reviews

The findings of this review are largely consistent with those published previously. Rydzewska 2017, Vale 2018 and Sathianathen 2019 all reported that abiraterone acetate with prednisolone plus ADT improved overall survival compared to ADT alone. It should be noted that Vale 2018 and Sathianathen 2019 were network meta-analyses that indirectly compared abiraterone acetate with prednisolone plus ADT to docetaxel plus ADT, and reported that it was most probable that abiraterone was the superior agent in this setting. The findings in this review are the most up to date, as it includes data that were not available previously, such as the subgroup analysis by the CHAARTED volume of disease criteria (James 2017).

AUTHORS' CONCLUSIONS

Implications for practice

The addition of abiraterone acetate with prednisolone to androgen deprivation therapy improves overall survival, and probably extends disease-specific survival and delays progression, compared to androgen deprivation therapy alone. It also results in a small improvement in quality of life at 12 months, but this is not clinically meaningful. However, grades III to V adverse events are increased, and probably more men discontinue treatment because of them. Therefore, men should be counseled about adverse events before commencing treatment, to help them understand the trade-offs of treatment.

Implications for research

Given our inability to conduct all of the pre-specified subgroup analyses, further research is required to define treatment effects across potential prognostic clinical characteristics, such as the volume of disease and prior treatment to the prostate. This would assist in identifying which men are more likely to experience the greatest benefit from upfront combination treatment with abiraterone acetate and ADT. The increasing use of prostate-specific membrane antigen-positron emission tomography (PSMA-PET) imaging globally warrants research in this setting, as it may impact classification in terms of volume of disease, and subsequently selection of men more likely to benefit.

Recently, there have been other agents that have been shown to be superior to ADT alone, to treat hormone-sensitive metastatic prostate cancer (Chi 2019; Davis 2019). Clinicians are currently relying predominantly on indirect evidence in deciding between these agents, but these estimates are not a substitute for direct evidence (Sathianathen 2019). Therefore, we need high quality head to head studies to determine which combination of treatment, if any, is superior to the others. Similarly, since multiple agents have demonstrated improvements over ADT alone in men with hormone sensitive prostate cancer, the cost of these agents should be considered when deciding which to use, especially in low-income settings (Sathianathen 2019a). Along these lines, additional research is required to identify the optimal sequence of treatment following progression, because there is evidence that shows that responsiveness to treatment following progression is dependent on previous exposure.

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REFERENCES

References to studies included in this review

Fizazi 2017 *{published and unpublished data}*

CHi K, Protheroe A, Rodriguez Antolin A, Facchini G, Suttman H, Matsubara N, et al. Benefits of abiraterone acetate plus prednisone (AA1P) when added to androgen deprivation therapy (ADT) in LATITUDE on patient (Pt) reported outcomes (PRO). *Annals of Oncology* 2017;**28**(Suppl 5):v269.

CHi K, Tran N, Feyerabend S, Matsubara N, Ozguroglu M, Fein LE, et al. Subsequent treatment after abiraterone acetate + prednisone (AA + P) in patients (pts) with newly diagnosed high-risk metastatic castration-naïve prostate cancer (NDx-HR mCNPC): detailed analyses from the phase 3 LATITUDE trial. *Journal of Clinical Oncology* 2018;**36**(15 Suppl 1):5028.

Chi KN, Protheroe A, Rodriguez-Antolin A, Facchini G, Suttman H, Matsubara N, et al. Patient-reported outcomes following abiraterone acetate plus prednisone added to androgen deprivation therapy in patients with newly diagnosed metastatic castration-naive prostate cancer (LATITUDE): an international, randomised phase 3 trial. *Lancet Oncology* 2018;**19**(2):194-206.

Feyerabend S, Saad F, Perualila NJ, Van Sanden S, Diels J, Ito T, et al. Adjusting overall survival estimates for treatment switching in metastatic, castration-sensitive prostate cancer: results from the LATITUDE study. *Target Oncology* 2019;**14**(6):681-8. [DOI: 0.1007/s11523-019-00685-x]

Fizazi K, Feyerabend S, Matsubara N, Ozguroglu M, Fein LE, Antolin AT. Longer term preplanned efficacy and safety analysis of abiraterone acetate plus prednisone (AA plus P) in patients (pts) with newly diagnosed high-risk metastatic castration-naive prostate cancer (NDx-HR mCNPC) from the phase 3 LATITUDE trial. *Journal of Clinical Oncology* 2018;**36**(15):5028.

Fizazi K, Larsen JS, Matheny S, Molina A, Li J, Todd MB, et al. Randomized double-blind, comparative study of abiraterone acetate (AA) plus low-dose prednisone (P) plus androgen deprivation therapy (ADT) versus ADT alone in newly diagnosed, high-risk, metastatic hormone-naive prostate cancer (mHNPC). *Journal of Clinical Oncology* 2013;**31**(15 Suppl 1):TPS5097.

Fizazi K, Tran N, Fein L, Matsubara N, Antolin AR, Alekseev BY, et al. LATITUDE: a phase III, double-blind, randomized trial of androgen deprivation therapy with abiraterone acetate plus prednisone or placebos in newly diagnosed high-risk metastatic hormone-naive prostate cancer. *Journal of Clinical Oncology* 2017;**35**(15 Suppl 1):LBA3.

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Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al, LATITUDE Investigators. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *New England Journal of Medicine* 2017;**377**(4):352-60.

Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. *Lancet Oncology* 2019;**20**(5):686-700.

Fizazi K, Tran N, Fein LE, Matsubara N, Bjartell A, Galli L. Abiraterone acetate (AA) plus prednisone (P) 5 mg QD in metastatic castration-naive prostate cancer (mCNPC): Detailed safety analyses from the LATITUDE phase 3 trial. *Journal of Clinical Oncology* 2018;**36**(6):182.

Fukasawa S, Suzuki H, Kawaguchi K, Noguchi H, Enjo K, Tran N, et al. Efficacy and safety of abiraterone acetate plus prednisone in Japanese patients with newly diagnosed, metastatic hormone-naive prostate cancer: a subgroup analysis of LATITUDE, a randomized, double-blind, placebo-controlled, phase 3 study. *Japanese Journal of Clinical Oncology* 2018;**48**(11):1012-21.

Fukasawa S, Suzuki H, Sato F, Hashine K, Hasumi H, Matsumoto H. Efficacy and safety of abiraterone acetate (AA) and low-dose prednisone (P) in Japanese patients with newly diagnosed, metastatic, hormone-naive prostate cancer (mHNPC): Subgroup analysis of LATITUDE trial. *Journal of Clinical Oncology* 2018;**36**(6):1012-21.

Li T, Franco-Villalobos C, Proskorovsky I, Sorensen SV, Tran N, Sulur G, et al. Medical resource utilization of abiraterone acetate plus prednisone added to androgen deprivation therapy in metastatic castration-naive prostate cancer: results from LATITUDE. *Cancer* 2019;**125**(4):626-32.

Li T, Franco-Villalobos C, Proskorovsky I, Sorensen SV, Tran N, Sulur G, et al. Medical resource utilization of abiraterone acetate plus prednisone added to androgen deprivation therapy in metastatic castration-naive prostate cancer: results from LATITUDE. *Cancer* 2019;**125**(4):626-32.

Li T, Franco-Villalobos C, Proskorovsky I, Sorensen SV, Tran N, Sulur G, et al. Medical resource utilization of abiraterone acetate plus prednisone added to androgen deprivation therapy in metastatic castration-naive prostate cancer: results from LATITUDE. *Journal of Clinical Oncology* 2018;**38**(6 Suppl 1):201.

Matsubara N, Chi KN, Özgüroğlu M, Rodriguez-Antolin A, Feyerabend S, Fein L, et al. Correlation of prostate-specific antigen kinetics with overall survival and radiological progression-free survival in metastatic castration-sensitive prostate cancer treated with abiraterone acetate plus prednisone or placebos added to androgen deprivation therapy: post hoc analysis of phase 3 LATITUDE study. *European Urology* 2020;**77**(4):494-500.

Matsubara N, Chi KN, Ozguroglu M, Antolin AR, Feyerabend S, Fein L, et al. LATITUDE study: PSA response characteristics and correlation with overall survival (OS) and radiological progression-free survival (rPFS) in patients with metastatic hormone-sensitive prostate cancer (mHSPC) receiving ADT plus abiraterone acetate and prednisone (AAP) or placebo (PBO). *Annals of Oncology* 2018;**28**:271-302.

Metin H, McQuarrie K, Thilakarathne P, Diels J, Ito T, Li T, et al. Benefit of abiraterone acetate plus prednisone (AA+P) added to

androgen deprivation therapy (ADT) in patients with high-risk, newly diagnosed metastatic hormone-sensitive prostate cancer (mHSPC): post hoc analysis of EQ-5D-5L from the latitude study. *Value in Health* 2018;**21 Suppl 1**:S38.

Suzuki H, Shin T, Fukasawa S, Hashine K, Kitani S, Ohtake N, et al. Efficacy and safety of abiraterone acetate plus prednisone in Japanese patients with newly diagnosed, metastatic hormone-naive prostate cancer: final subgroup analysis of LATITUDE, a randomized, double-blind, placebo-controlled, phase 3 study. *Japanese Journal of Clinical Oncology* 2020;**50**(7):810-20.

Woo H, Fizazi K, Sulur G, Tran N, Fein L, Matsubara N, et al. Final analysis of phase 3 LATITUDE study in patients (pts) with newly diagnosed high-risk metastatic castration-naive prostate cancer (NDx-HR mCNPC) treated with abiraterone acetate + prednisone (AA+P) added to androgen deprivation therapy (ADT). *BJU International* 2019;**123**(Suppl 2):27-8.

James 2017 *{published data only (unpublished sought but not used)}*

ClinicalTrialsgov. Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE). ClinicalTrials.gov 2005.

Hoyle AP, Ali A, James ND, Cook A, Parker CC, de Bono JS, et al. Abiraterone in "high-" and "low-risk" metastatic hormone-sensitive prostate cancer. *European Urology* 2019;**76**(6):719-28.

James ND, de Bono JS, Spears MR, Clarke N, Mason MD, Dearnaley D, et al. Adding abiraterone for men with high-risk prostate cancer (PCa) starting longterm androgen deprivation therapy (ADT): survival results from STAMPEDE (NCT00268476). *Journal of Clinical Oncology* 2017;**35**(18 Suppl):LBA5003.

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James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *New England Journal of Medicine* 2017;**377**(4):338-51.

References to studies excluded from this review

Buelens 2018 *{published data only}*

Buelens S, Poelaert F, Dhondt B, Fonteyne V, De Visschere P, Ost P, et al. Metastatic burden in newly diagnosed hormone-naive metastatic prostate cancer: comparing definitions of CHAARTED and LATITUDE trial. *Urologic Oncology: Seminars and Original Investigations* 2018;**36**(4):158.

Feyerabend 2018 *{published data only}*

Feyerabend S, Saad F, Li T, Ito T, Diels J, Sanden SV. Indirect treatment comparison (ITC) of abiraterone acetate (AA) plus prednisone (P) and docetaxel (DOC) on patient-reported outcomes (PROs) in metastatic castration-naive prostate cancer (mCNPC). *Journal of Clinical Oncology* 2018;**36**(Suppl 6):200.

Sydes 2017 *{published data only}*

Sydes MR, Mason MD, Spears MR, Clarke NW, Dearnaley D, Ritchie AWS, et al. Adding abiraterone acetate plus prednisolone (AAP) or docetaxel for patients (pts) with high-risk prostate cancer (PCa) starting long-term androgen deprivation therapy (ADT): Directly randomised data from STAMPEDE (NCT00268476). *Annals of Oncology* 2017;**28**(Suppl 5):v619.

Sydes MR, Spears MR, Mason MD, Clarke NW, Dearnley DP, de Bono JS. Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: directly randomised data from the STAMPEDE multi-arm, multi-stage platform protocol. *Annals of Oncology* 2018;**29**(5):1235-48.

Additional references

Attard 2008

Attard G, Reid AH, Yap TA, Raynaud F, Dowsett M, Settatree S, et al. Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. *Journal of Clinical Oncology* 2008;**26**(28):4563-71.

Beer 2014

Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *New England Journal of Medicine* 2014;**371**(5):424-33.

Berruti 2005

Berruti A, Tucci M, Mosca A, Tarabuzzi R, Gorzegno G, Terrone C, et al. Predictive factors for skeletal complications in hormone-refractory prostate cancer patients with metastatic bone disease. *British Journal of Cancer* 2005;**93**(6):633-8.

Cella 2009

Cella D, Nichol MB, Eton D, Nelson JB, Mulani P. Estimating clinically meaningful changes for the functional assessment of cancer therapy – prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. *Value in Health* 2009;**12**(1):124-9.

Chi 2019

Chi KM, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *New England Journal of Medicine* 2019;**381**:13-24.

Davis 2019

Davis ID, Martin AJ, Stockler MR, Begbie S, Kim KN, Chowdhury S, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *New England Journal of Medicine* 2019;**381**:121-31.

de Bono 2010

de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al, TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010;**376**(9747):1147-54.

de Bono 2011

de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in

metastatic prostate cancer. *New England Journal of Medicine* 2011;**364**(21):1995-2005.

Deeks 2011

Deeks JJ, Higgins JP, Altman DG, editor(s). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/cochrane-handbook.

EndNote 2016 [Computer program]

EndNote. Version 7.5. Philadelphia (PA): Clarivate Analytics, 2016. Available at endnote.com.

Fizazi 2012

Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncology* 2012;**13**(10):983-92.

Gillessen 2015

Gillessen S, Omlin A, Attard G, de Bono JS, Efstathiou E, Fizazi K, et al. Management of patients with advance prostate cancer: recommendations of the St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) 2015. *Annals of Oncology* 2015;**26**(8):1589-604.

GRADEpro GDT [Computer program]

GRADEpro GDT. Version accessed prior to 04 July 2020. Hamilton (ON): McMaster University (developed by Evidence Prime), N/A. Available at gradepro.org.

Guyatt 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Schünemann HJ, et al. What is "quality of evidence" and why is it important to clinicians? *BMJ (Clinical Research Ed.)* 2008;**336**(7651):995-8. [DOI: 10.1136/bmj.39490.551019.BE]

Guyatt 2011

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction – GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383-94. [DOI: 10.1016/j.jclinepi.2010.04.026]

Hamdy 2016

Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *New England Journal of Medicine* 2016;**375**(15):1415-24.

Heinlein 2004

Heinlein CA, Chang C. Androgen receptor in prostate cancer. *Endocrine Reviews* 2004;**25**(2):276-308.

Higgins 2002

Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;**21**(11):1539-58. [DOI: 10.1002/sim.1186]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ (Clinical Research Ed.)* 2003;**327**(7414):557-60. [DOI: 10.1136/bmj.327.7414.557]

Higgins 2011a

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/cochrane-handbook.

Higgins 2011b

Higgins JP, Altman DG, Sterne JA, editor(s). Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/cochrane-handbook.

Huggins 1941

Huggins C, Stevens RE Jr, Hodges C V. Studies on prostatic cancer: Ii. the effects of castration on advanced carcinoma of the prostate gland. *Archives of Surgery* 1941;**43**(2):209-23.

Inoue 2009

Inoue T, Segawa T, Kamba T, Yoshimura K, Nakamura E, Nishiyama H, et al. Prevalence of skeletal complications and their impact on survival of hormone refractory prostate cancer patients in Japan. *Urology* 2009;**73**(5):1104-9.

James 2015

James ND, Spears MR, Clarke NW, Dearnaley DP, De Bono JS, Gale J, et al. Survival with newly diagnosed metastatic prostate cancer in the "Docetaxel Era": data from 917 patients in the control arm of the STAMPEDE trial (MRC PR08, CRUK/06/019). *European Urology* 2015;**67**(6):1028-38.

James 2016

James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016;**387**(10024):1163-77.

Janknegt 1997

Janknegt RA, Boon TA, van de Beek C, Grob P. Combined hormono/chemotherapy as primary treatment for metastatic prostate cancer: a randomized, multicenter study of orchiectomy alone versus orchiectomy plus estramustine phosphate. The Dutch Estracyt Study Group. *Urology* 1997;**49**(3):411-20.

Kantoff 2010

Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *New England Journal of Medicine* 2010;**363**(5):411-22.

Liberati 2009

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Medicine* 2009;**6**(7):e1000100. [DOI: 10.1371/journal.pmed.1000100]

Millikan 2008

Millikan RE, Wen S, Pagliaro LC, Brown MA, Moomey B, Do KA, et al. Phase III trial of androgen ablation with or without three cycles of systemic chemotherapy for advanced prostate cancer. *Journal of Clinical Oncology* 2008;**26**(36):5936-42.

Murphy 1983

Murphy GP, Beckley S, Brady MF, Ming Chu T, Dekernion JB, Dhabuwala C, et al. Treatment of newly diagnosed metastatic prostate cancer patients with chemotherapy agents in combination with hormones versus hormones alone. *Cancer* 1983;**51**(7):1264-72.

Petrylak 2004

Petrylak DP, Tangen CM, Hussain MH, Lara PN Jr, Jones JA, Taplin ME, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *New England Journal of Medicine* 2004;**351**(15):1513-20.

Pummer 1997

Pummer K, Lehnert M, Stettner H, Hubmer G. Randomized comparison of total androgen blockade alone versus combined with weekly epirubicin in advanced prostate cancer. *European Urology* 1997;**32 Suppl 3**:81-5.

Rawla 2019

Rawla P. Epidemiology of Prostate Cancer. *World J Oncol* 2019;**10**(2):63-89.

Review Manager 2014 [Computer program]

Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Ryan 2013

Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *New England Journal of Medicine* 2013;**368**(2):138-48.

Ryan 2015

Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PF, Sternberg CN, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncology* 2015;**16**(2):152-60.

Rydzewska 2017

Rydzewska LH, Burdett S, Vale CL, Clarke NW, Fizazi K, Kheoh T, et al. Adding abiraterone to androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: a systematic review and meta-analysis. *European Journal of Cancer* 2017;**84**:88-101.

Sathianathen 2017

Sathianathen NJ, Philippou YA, Kuntz GM, Konety BR, Lamb AD, Dahm P. Taxane-based chemohormonal therapy for metastatic hormone-sensitive prostate cancer. *Cochrane Database of Systematic Reviews* 2017, Issue 9. Art. No: CD012816. [DOI: 10.1002/14651858.CD012816]

Sathianathen 2018

Sathianathen NJ, Philippou YA, Kuntz GM, Konety BR, Gupsta S, Lamb AD, et al. Taxane-based chemohormonal therapy for metastatic hormone-sensitive prostate cancer. *Cochrane Database of Systematic Reviews* 2018, Issue 10. Art. No: CD012816. [DOI: 10.1002/14651858.CD012816.pub2]

Sathianathen 2019

Sathianathen NJ, Koschel S, Thangasamy IA, Teh J, Alghazo O, Butcher G, et al. Indirect comparisons of efficacy between combination approaches in metastatic hormone-sensitive prostate cancer: a systematic review and network meta-analysis. *European Urology* 2019;**77**(3):365-72. [DOI: 10.1016/j.eururo.2019.09.004] [PMID: 31679970]

Sathianathen 2019a

Sathianathen NJ, Alarid-Escudero F, Kuntz KM, Lawrentschuk N, Bolton DM, Kim SP et al. A cost-effectiveness analysis of systemic therapy for metastatic hormone-sensitive prostate cancer. *European Urology Oncology* 2019;**2**(6):649-55.

Scher 2008

Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *Journal of Clinical Oncology* 2008;**26**(7):1148-59.

Scher 2012

Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *New England Journal of Medicine* 2012;**367**(13):1187-97.

Schünemann 2011

Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JP, Green S, editor(s), Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/cochrane-handbook.

Siegel 2018

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA: a Cancer Journal for Clinicians* 2018;**68**(1):7-30.

Soifer 2012

Soifer HS, Souleimanian N, Wu S, Voskresenskiy AM, Collak FK, Cinar B, et al. Direct regulation of androgen receptor activity by potent CYP17 inhibitors in prostate cancer cells. *Journal of Biological Chemistry* 2012;**287**(6):3777-87.

Sweeney 2015

Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *New England Journal of Medicine* 2015;**373**(8):737-46.

Tannock 2004

Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *New England Journal of Medicine* 2004;**351**(15):1502-12.

Tilki 2016

Tilki D, Schaeffer EM, Evans CP. Understanding mechanisms of resistance in metastatic castration-resistant prostate cancer: the role of the androgen receptor. *European Urology Focus* 2016;**2**(5):499-505.

Torre 2015

Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA: a Cancer Journal for Clinicians* 2015;**65**(2):87-108.

Vale 2018

Vale CL, Fisher DJ, White IR, Carpenter JR, Burdett S, Clarke NW, et al. What is the optimal systemic treatment of men with metastatic, hormone-naive prostate cancer? A STOPCAP systematic review and network meta-analysis. *Annals of Oncology* 2018;**29**(5):1249-57.

Wallis 2018

Wallis CJ, Klaassen Z, Bhindi B, Goldberg H, Chandrasekar T, Farrell AM, et al. Comparison of abiraterone acetate and docetaxel with androgen deprivation therapy in high-risk and metastatic hormone-naive prostate cancer: a systematic review and network meta-analysis. *European Urology* 2018;**73**(6):834-44.

Zelefsky 2010

Zelefsky MJ, Eastham JA, Cronin AM, Fuks Zi, Zhang Z, Yamada Y, et al. Metastasis after radical prostatectomy or external beam radiotherapy for patients with clinically localized prostate cancer: a comparison of clinical cohorts adjusted for case mix. *Journal of Clinical Oncology* 2010;**28**(9):1508-13.

References to other published versions of this review

Sathianathen 2019b

Sathianathen NJ, Oestreich MC, Brown SJane, Gupta S, Konety BR, Dahm P, Kunath F. Abiraterone acetate in combination with androgen deprivation therapy compared to androgen deprivation therapy only for metastatic hormone-sensitive prostate cancer. *Cochrane Database of Systematic Reviews* 2019, Issue 1. Art. No: CD013245. [DOI: 10.1002/14651858.CD013245]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Fizazi 2017

Study characteristics	
Methods	Study design: parallel arm, double-blind, placebo-controlled Setting/country: 235 sites in 34 countries in Europe, the Asia–Pacific region, Latin America, and Canada Dates when study was conducted: randomization conducted from 12 February 2013 to 11 December 2014
Participants	Inclusion criteria: • Willing and able to provide written, informed consent • Men aged 18 years and older • Newly diagnosed metastatic prostate cancer within 3 months prior to randomization • Adenocarcinoma of the prostate confirmed by histology or cytology without neuroendocrine differentiation or small cell histology • Distant metastatic disease documented by positive bone scan or metastatic lesions on CT or MRI • Two of the following high-risk prognostic factors: Gleason score ≥ 8, presence of 3 or more lesions on bone scan, presence of measurable visceral (excluding lymph node disease) metastasis (RECIST 1.1) • Eastern Cooperative Oncology Group (ECOG) performance status grade of 0, 1, or 2 • Adequate hematologic, hepatic, and renal function • Ability to swallow study medication tablets • Agrees to use a condom and another effective method of birth control if having sex with a woman of childbearing potential

Fizazi 2017 *(Continued)*

Exclusion criteria:

- Active infection or other medical condition that would contraindicate use of prednisone
- Any chronic medical condition requiring a higher systemic dose of corticosteroid than 5 mg prednisone per day
- Pathological finding consistent with small cell carcinoma of the prostate
- Known brain metastasis
- Any prior pharmacotherapy, radiation therapy, or surgery with curative intent for metastatic prostate cancer. The following exceptions were allowed: up to 3 months of ADT with LHRH agonists or orchiectomy, with or without concurrent anti-androgens, prior to the men's randomization was permitted; men may have one course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease (e.g. impending cord compression or obstructive symptoms) if it was administered prior to randomization. Radiation or surgical therapy could not have been initiated 4 weeks after the start of ADT or orchiectomy
- Uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic BP ≥ 95 mmHg)
- Men with a history of hypertension were allowed, provided blood pressure was controlled by anti-hypertensive treatment
- Active or symptomatic viral hepatitis or chronic liver disease
- History of adrenal dysfunction
- Clinically significant heart disease, as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class II to IV heart disease, or cardiac ejection fraction measurement of < 50% at baseline
- Atrial fibrillation, or other cardiac arrhythmia requiring pharmacotherapy
- Other malignancy (within 5 years), except non-melanoma skin cancer
- Administration of an investigational therapeutic or invasive surgical procedure (not including surgical castration) within 30 days of cycle 1, day 1, or currently enrolled in an investigational study
- Any condition or situation, which in the opinion of the investigator, would put the man at risk, may confound study results, or interfere with the man's participation in this study

Total number of men randomly assigned: 1199

Group A (abiraterone acetate + ADT)

Number of men randomly assigned: 597

Age: median 68 years (range 38 to 89)

Median prostate specific antigen (PSA): not reported

Prior local therapy: not reported

High-volume disease: not reported

Group B (ADT only)

Number of men randomly assigned: 602

Age: median 67 years (range 33 to 92)

Median PSA: not reported

Prior local therapy: not reported

High-volume disease: not reported

Interventions	**Group A**: androgen deprivation therapy and abiraterone acetate (1000 mg daily, given once daily as four 250 mg tablets) and prednisone (5 mg daily) in addition to androgen deprivation therapy **Group B:** androgen deprivation therapy and placebo

Fizazi 2017 *(Continued)*

	Duration: men who had not undergone surgical castration received ongoing androgen deprivation therapy to reach or maintain a serum testosterone level of less than 50 ng/dL (1.7 nmol/L)
Outcomes	Primary: • Overall survival: defined as the time from randomization to date of death from any cause Secondary: • Radiographic progression-free survival (rPFS): based on Prostate Cancer Working Group 2 (PCWG2) and modified RECIST, as the time from randomization to the occurrence of one of the following: (i) bone scan, if the first bone scan with ≥ 2 new lesions compared to baseline was observed ≥ 16 weeks (cycle 5, day 1) from randomization. If the ≥ 2 new lesions were noted at or before cycle 5, day 1, a confirmatory bone scan was performed ≥ 6 weeks later (to eliminate a false progression that could potentially be a flare phenomenon); or (ii) progression of soft tissue lesions measured by CT or MRI, defined in modified RECIST criteria; or (iii) death from any cause • Time to next skeletal-related event: clinical fracture, spinal cord compression, palliative radiation to bone, or surgery to bone • Time to PSA progression • Time to next subsequent therapy for prostate cancer • Time to initiation of chemotherapy Exploratory end points: • PSA response rate • Patient-reported outcome (PRO) measures: EQ-5D-5L, BPI-SF, FACT-P, BFI • Pain measures (time to pain progression) • Time to symptomatic local progression, defined as occurrence of urethral obstruction or bladder outlet obstruction • Prostate cancer-specific survival
Funding sources	Janssen Research and Development
Declarations of interest	Multiple relationships with industry amongst several study authors
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generated centrally by an independent, uninvolved, third-party: Methods: "country-by country randomisation scheme was implemented by permuted block randomisation (with two blocks). The randomisation schedule was prepared by an independent statistician who was otherwise not involved with the study"
Allocation concealment (selection bias)	Low risk	Randomization performed centrally. "Randomization will take place across all study sites using a centralized Interactive Web/Voice Response System (IWRS/IVRS)."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled, phase 3 trial

Fizazi 2017 *(Continued)*

Blinding of outcome assessment (detection bias) Time to death due to any cause	Low risk	Objective outcome that is unlikely to be affected by blinding
Blinding of outcome assessment (detection bias) Quality of life	Low risk	Quality of life measured through self-assessed questionnaires completed by men who were blinded to their treatment
Blinding of outcome assessment (detection bias) Grades III to V adverse events	Low risk	Blinded investigator determined severity: "The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (e.g. laboratory abnormalities)."
Blinding of outcome assessment (detection bias) Time to death due to prostate cancer	Unclear risk	No information provided on who was responsible for determining the cause of death, and whether they were blinded.
Blinding of outcome assessment (detection bias) Time to disease progression	Low risk	Individuals involved in the determination of progression (using radiology, PSA, or both) were blinded.
Blinding of outcome assessment (detection bias) Discontinued treatment due to adverse events	Low risk	Although not clearly specified, the reason for discontinuing treatment was likely to be reported by investigators who were blinded to treatment allocation.
Incomplete outcome data (attrition bias) Oncological outcomes	Low risk	All of the men were analyzed in the groups to which they were randomised, with no loss to follow-up.
Incomplete outcome data (attrition bias) Quality of life	High risk	From the additional data received from the study authors, only 469/597 (78.5%) men in the abiraterone acetate group and 369/610 (72.3%) men in the control group completed FACT-P questionnaires at 12 months.
Incomplete outcome data (attrition bias) Toxicity outcomes	Low risk	All of the men were analyzed in the groups to which they were randomised, with no loss to follow-up.
Selective reporting (reporting bias)	Low risk	Outcomes were reported as described in the protocol.
Other bias	Low risk	No other source of bias identified

James 2017

Study characteristics	
Methods	Study design: 5-stage multi-arm, open-label, randomized controlled trial Setting/country: 111 U.K. and 5 Swiss sites Dates when study was conducted: randomization between November 2011 and January 2014
Participants	Inclusion criteria:

James 2017 *(Continued)*

- High risk newly diagnosed men with one of: (i) stage T3/4 N0 M0 histologically confirmed prostate adenocarcinoma with PSA ≥ 40 ng/mL or Gleason sum score 8 to 10; (ii) stage Tany N+ M0 or Tany Nany M+ histologically confirmed prostate adenocarcinoma; (iii) multiple sclerotic bone metastases with a PSA ≥ 100 ng/mL without histological confirmation; or men with histologically confirmed prostate adenocarcinoma previously treated with radical surgery or radiotherapy who are now relapsing with one of: (i) PSA ≥ 4 ng/mL and rising, with doubling time less than 6 months; (ii) PSA ≥ 20 ng/mL
- Intention to treat with long-term androgen suppression
- Fit for all protocol treatment and follow-up, WHO performance status 0 to 2
- Have completed the appropriate investigations prior to randomization
- Adequate haematological function: neutrophil count > 1.5 x 109/L and platelets > 100 x 109/L
- Adequate renal function: serum creatinine < 1.5 ULN
- Adequate liver function: ALT or AST < 1.5 ULN, bilirubin < ULN
- Normal testosterone level prior to hormone treatment
- Written informed consent
- Willing and expected to comply with follow-up schedule

Exclusion criteria:

- Prior systemic therapy for locally advanced or metastatic prostate cancer except those listed in inclusion criteria 1
- Metastatic brain disease or leptomeningeal disease
- Any other previous, or current malignant disease, which in the judgement of the responsible physician, is likely to interfere with STAMPEDE treatment or assessment
- Symptomatic peripheral neuropathy grade 2 (NCI CTC)
- Any surgery (e.g. TURP) performed within the past 4 weeks

Total number of men randomly assigned: 1917 (1002 with metastatic disease)

Group A (abiraterone acetate + ADT)

Number of men randomly assigned: 960 (500 with metastatic disease)

Age: median 67 years (range 42 to 85)

Median PSA: 51 (IQR 19 to 158)

Prior local therapy: 60 (35 with metastatic disease)

High-volume disease: not reported

Group B (ADT only)

Number of men randomly assigned: 957 (502 with metastatic disease)

Age: median 67 years (range 39 to 84)

Median PSA: median 56 (IQR 19 to 165)

Prior local therapy: 38 (26 with metastatic disease)

High-volume disease: not reported

Interventions	**Group A**: abiraterone (1000 mg) with prednisolone (5 mg) was given once daily in addition to androgen deprivation therapy, through either bilateral orchidectomy or luteinizing hormone releasing hormone agonists **Group B**: androgen deprivation therapy, through either bilateral orchidectomy or luteinizing hormone releasing hormone agonists

James 2017 *(Continued)*

	Duration: abiraterone and prednisolone treatment continued until PSA, radiologic, or clinical progression, or until another treatment was started. Androgen deprivation therapy was administered for at least for two years.
Outcomes	Primary: • Overall survival Secondary: • Quality of life • Cost effectiveness • Failure-free survival • Toxicity • Skeletal-related events
Funding sources	Cancer Research U.K. (CRUK_A12459), Medical Research Council (MRC_MC_UU_12023/25), Astellas Pharma, Clovis Oncology, Janssen, Novartis, Pfizer, and Sanofi-Aventis.
Declarations of interest	Multiple relationships with industry amongst several trial authors
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer algorithm was used to create sequence.
Allocation concealment (selection bias)	Low risk	Central allocation used to conceal allocation "Randomization was performed centrally by telephone with the use of a computerized algorithm, which was developed and maintained by the MRC Clinical Trials Unit at UCL"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial described in methods
Blinding of outcome assessment (detection bias) Time to death due to any cause	Low risk	Objective outcome that was unlikely to be affected by blinding
Blinding of outcome assessment (detection bias) Quality of life	High risk	QoL measured through self-assessment questionnaires, completed by men who were not blinded to their treatment
Blinding of outcome assessment (detection bias) Grades III to V adverse events	High risk	Adverse events graded by unblinded investigator. "When an AE/AR occurs, the investigator responsible for the care of the patient must first assess whether the event is serious using the definitions given"
Blinding of outcome assessment (detection bias) Time to death due to prostate cancer	Low risk	Cause of death determined by blinded reviewer

James 2017 *(Continued)*

Blinding of outcome assessment (detection bias) Time to disease progression	Unclear risk	No data on whether assessors of time-to-progression were blinded, and outcome susceptible to detection bias
Blinding of outcome assessment (detection bias) Discontinued treatment due to adverse events	Unclear risk	No information on whether assessor determining the reason for discontinuing treatment was blinded
Incomplete outcome data (attrition bias) Oncological outcomes	Low risk	All the men were included in the efficacy analyses under their assigned treatment on an intention-to-treat basis.
Incomplete outcome data (attrition bias) Quality of life	Low risk	Not reported
Incomplete outcome data (attrition bias) Toxicity outcomes	Low risk	All the men were included in the efficacy analyses under their assigned treatment on an intention-to-treat basis.
Selective reporting (reporting bias)	High risk	QoL stated as secondary outcome of trial, but not reported.
Other bias	Low risk	No other source of bias identified.

CT: computer tomography
MRI: magnetic resonance imaging
RECIST 1.1: response evaluation criteria in solid tumors 1.1
ADT with LHRH: androgen deprivation therapy with luteinizing hormone-releasing hormone
PSA: prostate specific antigen
BPI-SF: Brief Pain Inventory - Short Form
FACT-P: Functional Assessment of Cancer Therapy – Prostate
BFI: Brief Fatigue Inventory
ALT: alanine aminotransferase
AST: aspartate transaminase
ULN: upper limit of normal
WHO: World Health Organisation
NCI CTC: National Cancer Institute Common Terminology Criteria for Adverse Events
TURP: transurethral resection of prostate
IQR: interquartile range
QoL: quality of life

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Buelens 2018	Wrong study design
Feyerabend 2018	Wrong comparator: abiraterone acetate + ADT vs docetaxel + ADT
Sydes 2017	Wrong comparator: abiraterone acetate + ADT vs docetaxel + ADT

ADT: androgen deprivation therapy

DATA AND ANALYSES

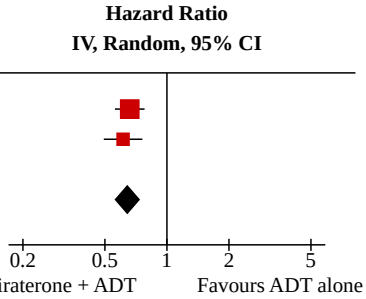
Comparison 1. Abiraterone + ADT vs ADT alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Time to death due to any cause	2		Hazard Ratio (IV, Random, 95% CI)	0.64 [0.56, 0.73]
1.2 Quality of life	1	838	Mean Difference (IV, Random, 95% CI)	2.90 [0.11, 5.69]
1.3 Grades III to V adverse events	1	1199	Risk Ratio (M-H, Random, 95% CI)	1.34 [1.22, 1.47]
1.4 Time to death due to prostate cancer	2		Hazard Ratio (IV, Random, 95% CI)	0.58 [0.50, 0.68]
1.5 Time to disease progression	2		Hazard Ratio (IV, Random, 95% CI)	0.35 [0.26, 0.49]
1.6 Discontinued treatment due to adverse events	1	1199	Risk Ratio (M-H, Random, 95% CI)	1.50 [1.17, 1.92]

Analysis 1.1. Comparison 1: Abiraterone + ADT vs ADT alone, Outcome 1: Time to death due to any cause

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Fizazi 2017	-0.415515444	0.084529882	62.9%	0.66 [0.56 , 0.78]
James 2017	-0.49	0.11	37.1%	0.61 [0.49 , 0.76]
Total (95% CI)			**100.0%**	**0.64 [0.56 , 0.73]**

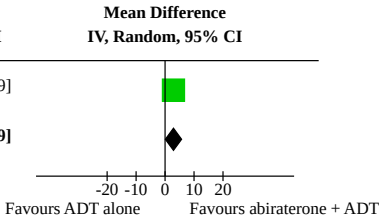
Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 6.61 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Abiraterone + ADT vs ADT alone, Outcome 2: Quality of life

Study or Subgroup	Abiraterone + ADT Mean	SD	Total	ADT alone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fizazi 2017	118.97	20.3882	469	116.069	20.56	369	100.0%	2.90 [0.11 , 5.69]
Total (95% CI)			**469**			**369**	**100.0%**	**2.90 [0.11 , 5.69]**

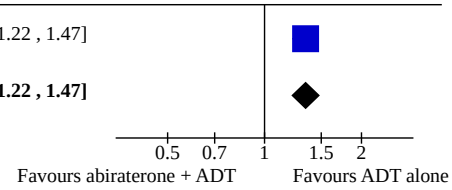
Heterogeneity: Not applicable
Test for overall effect: Z = 2.04 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Abiraterone + ADT vs ADT alone, Outcome 3: Grades III to V adverse events

Study or Subgroup	Abiraterone + ADT Events	Total	ADT alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fizazi 2017	411	597	309	602	100.0%	1.34 [1.22 , 1.47]
Total (95% CI)		**597**		**602**	**100.0%**	**1.34 [1.22 , 1.47]**
Total events:	411		309			

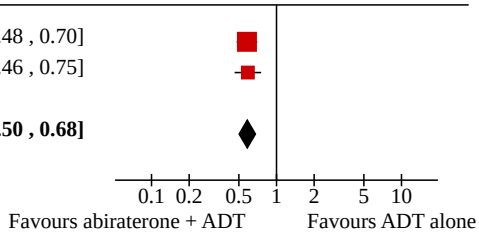
Heterogeneity: Not applicable
Test for overall effect: Z = 6.08 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Abiraterone + ADT vs ADT alone, Outcome 4: Time to death due to prostate cancer

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Fizazi 2017	-0.5447	0.0966	62.5%	0.58 [0.48 , 0.70]
James 2017	-0.52763274	0.1247058	37.5%	0.59 [0.46 , 0.75]
Total (95% CI)			**100.0%**	**0.58 [0.50 , 0.68]**

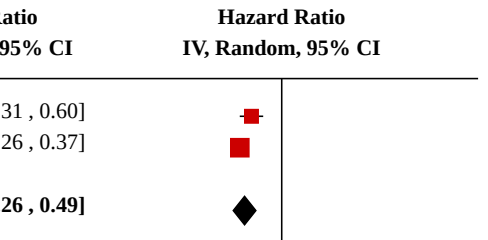
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 7.05 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Abiraterone + ADT vs ADT alone, Outcome 5: Time to disease progression

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Fizazi 2017	-0.844	0.1669	40.7%	0.43 [0.31 , 0.60]
James 2017	-1.17	0.09	59.3%	0.31 [0.26 , 0.37]
Total (95% CI)			**100.0%**	**0.35 [0.26 , 0.49]**

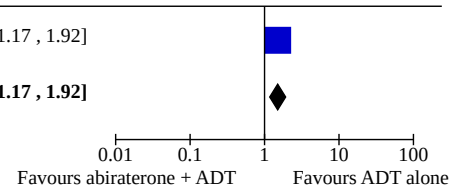
Heterogeneity: Tau² = 0.04; Chi² = 2.96, df = 1 (P = 0.09); I² = 66%
Test for overall effect: Z = 6.48 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Abiraterone + ADT vs ADT alone, Outcome 6: Discontinued treatment due to adverse events

Study or Subgroup	Abiraterone + ADT Events	Total	ADT alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Fizazi 2017	131	597	88	602	100.0%	1.50 [1.17 , 1.92]
Total (95% CI)		**597**		**602**	**100.0%**	**1.50 [1.17 , 1.92]**
Total events:	131		88			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.25 (P = 0.001)
Test for subgroup differences: Not applicable

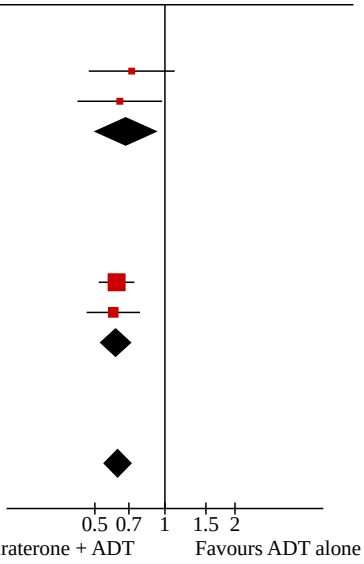


Comparison 2. Subgroup analysis: volume of metastases

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Time to death due to any cause	2		Hazard Ratio (IV, Random, 95% CI)	0.63 [0.55, 0.71]
2.1.1 Low volume metastases	2		Hazard Ratio (IV, Random, 95% CI)	0.68 [0.50, 0.91]
2.1.2 High volume metastases	2		Hazard Ratio (IV, Random, 95% CI)	0.61 [0.53, 0.71]
2.2 Quality of life	1	838	Mean Difference (IV, Random, 95% CI)	2.45 [-2.15, 7.05]
2.2.1 Low volume metastases	1	81	Mean Difference (IV, Random, 95% CI)	-2.03 [-10.98, 6.92]
2.2.2 High volume metastases	1	757	Mean Difference (IV, Random, 95% CI)	3.68 [0.73, 6.63]
2.3 Time to death due to prostate cancer	2		Hazard Ratio (IV, Random, 95% CI)	0.58 [0.51, 0.68]
2.3.1 Low volume metastases	2		Hazard Ratio (IV, Random, 95% CI)	0.67 [0.44, 1.01]
2.3.2 High volume metastases	2		Hazard Ratio (IV, Random, 95% CI)	0.57 [0.49, 0.67]
2.4 Time to disease progression	2		Hazard Ratio (IV, Random, 95% CI)	0.46 [0.36, 0.58]
2.4.1 Low volume metastases	2		Hazard Ratio (IV, Random, 95% CI)	0.46 [0.33, 0.63]
2.4.2 High volume metastases	2		Hazard Ratio (IV, Random, 95% CI)	0.46 [0.31, 0.69]

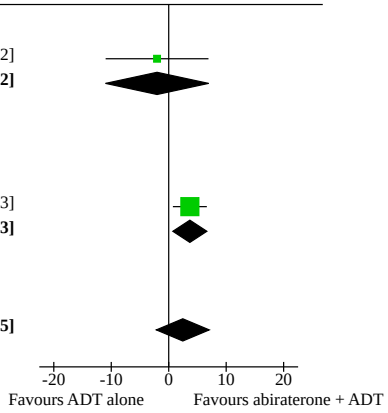
Analysis 2.1. Comparison 2: Subgroup analysis: volume of metastases, Outcome 1: Time to death due to any cause

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
2.1.1 Low volume metastases				
Fizazi 2017	-0.328504067	0.216921623	9.6%	0.72 [0.47 , 1.10]
James 2017	-0.446287103	0.21353096	9.9%	0.64 [0.42 , 0.97]
Subtotal (95% CI)			**19.5%**	**0.68 [0.50 , 0.91]**
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%				
Test for overall effect: Z = 2.55 (P = 0.01)				
2.1.2 High volume metastases				
Fizazi 2017	-0.478035801	0.090005453	55.7%	0.62 [0.52 , 0.74]
James 2017	-0.510825624	0.134711079	24.9%	0.60 [0.46 , 0.78]
Subtotal (95% CI)			**80.5%**	**0.61 [0.53 , 0.71]**
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%				
Test for overall effect: Z = 6.52 (P < 0.00001)				
Total (95% CI)			**100.0%**	**0.63 [0.55 , 0.71]**
Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 3 (P = 0.91); I² = 0%				
Test for overall effect: Z = 6.98 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.35, df = 1 (P = 0.56), I² = 0%				

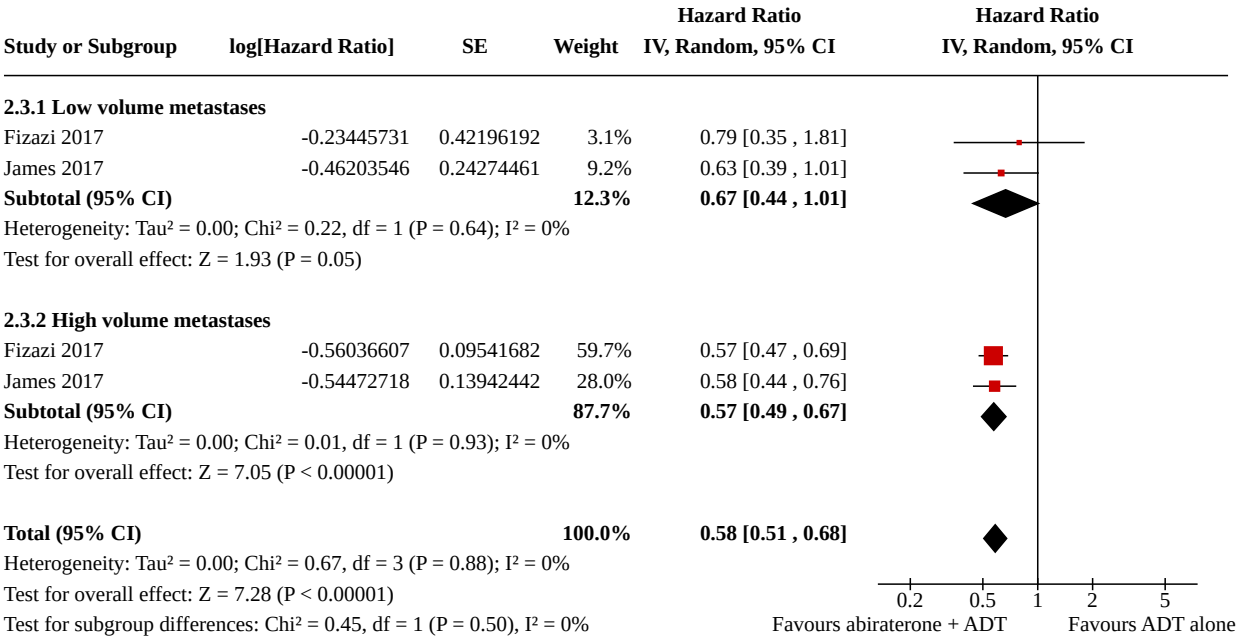


Analysis 2.2. Comparison 2: Subgroup analysis: volume of metastases, Outcome 2: Quality of life

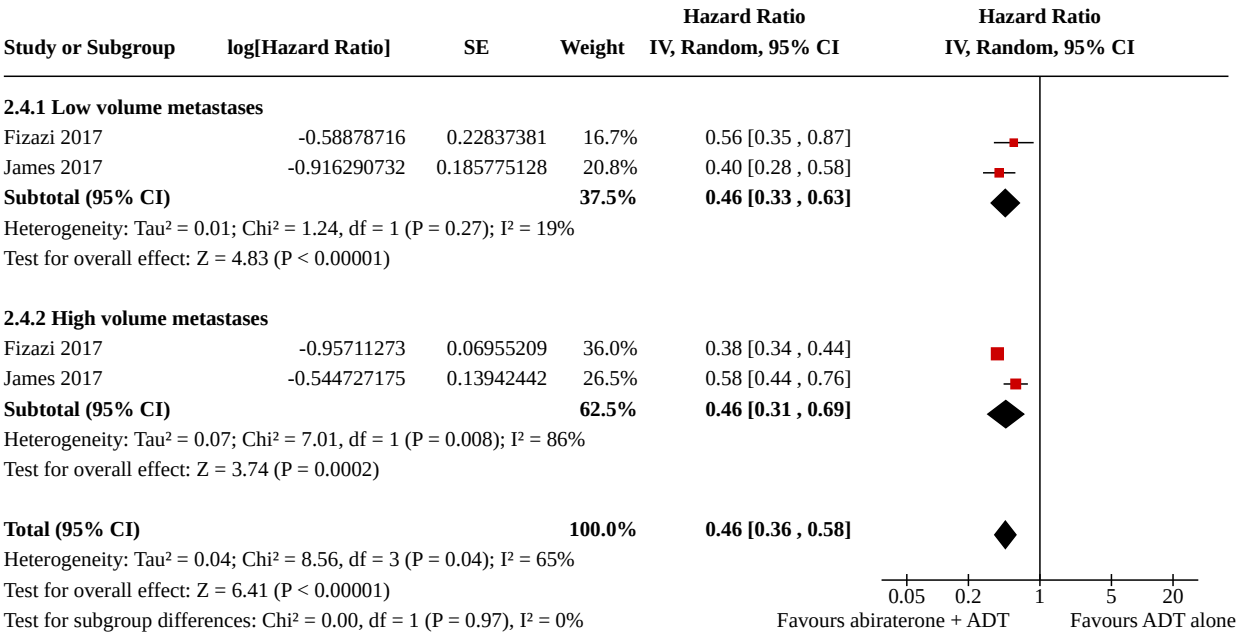
Study or Subgroup	Abiraterone + ADT Mean	SD	Total	ADT alone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.2.1 Low volume metastases								
Fizazi 2017	120.58	21.667	36	122.61	18.75	45	21.5%	-2.03 [-10.98 , 6.92]
Subtotal (95% CI)			**36**			**45**	**21.5%**	**-2.03 [-10.98 , 6.92]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.44 (P = 0.66)								
2.2.2 High volume metastases								
Fizazi 2017	118.84	20.299	433	115.16	20.666	324	78.5%	3.68 [0.73 , 6.63]
Subtotal (95% CI)			**433**			**324**	**78.5%**	**3.68 [0.73 , 6.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.44 (P = 0.01)								
Total (95% CI)			**469**			**369**	**100.0%**	**2.45 [-2.15 , 7.05]**
Heterogeneity: Tau² = 4.74; Chi² = 1.41, df = 1 (P = 0.24); I² = 29%								
Test for overall effect: Z = 1.05 (P = 0.30)								
Test for subgroup differences: Chi² = 1.41, df = 1 (P = 0.24), I² = 29.1%								



Analysis 2.3. Comparison 2: Subgroup analysis: volume of metastases, Outcome 3: Time to death due to prostate cancer



Analysis 2.4. Comparison 2: Subgroup analysis: volume of metastases, Outcome 4: Time to disease progression



ADDITIONAL TABLES

Table 1. Description of interventions

Study	Interventions (route, frequency, total dose/day)	Comparators (route, frequency, total dose/day)
LATITUDE (Fizazi 2017)	I1: abiraterone acetate (1000 mg daily, given once daily as four 250 mg tablets) and prednisone (5 mg daily) in addition to ADT, given through either bilateral orchidectomy or luteinizing hormone releasing hormone (LHRH) agonists	C1: ADT alone, given through either bilateral orchidectomy or LHRH agonists
STAMPEDE (James 2017)	I1: abiraterone (1000 mg) with prednisolone (5 mg), given once daily in addition to ADT, given through LHRH agonists or antagonists, bilateral orchidectomy, combined androgen blockade	C1: ADT alone, given through LHRH agonists or antagonists, bilateral orchidectomy, combined androgen blockade

ADT: androgen deprivation therapy; C: comparator; I: intervention

Table 2. Baseline characteristics

Study	Intervention and comparator	Duration of follow-up	Number of participants	Median age	Prior local therapy (%)	Gleason 8 to 10 (%)
Fizazi 2017	I1: abiraterone acetate (1000 mg daily, given once daily as four 250 mg tablets) and prednisone (5 mg daily) in addition to ADT[a]	5 years	597	68 years (range 38 to 89)	NR	98
	C1: ADT alone[a]		602	67 years (range 33 to 92)	NR	97
James 2017	I1: abiraterone (1000 mg) with prednisolone (5 mg), given once daily in addition to ADT[a]	Until death of all randomised men	500	67 years (range 42 to 85)	7	NR
	C1: ADT alone[a]		502	67 years (range 39 to 84)	5	NR

NR: not reported
ADT: androgen deprivation therapy
C: comparator; I: intervention; SD: standard deviation

[a]The following therapies were classified as ADT: luteinizing hormone releasing hormone agonists or antagonists, bilateral orchidectomy, combined androgen blockade

APPENDICES

Appendix 1. Cochrane Library search strategy

#1 MeSH descriptor: [Prostatic Neoplasms] explode all trees 4723

#2 MeSH descriptor: [Prostatic Intraepithelial Neoplasia] explode all trees 44

#3 (prostatic intraepithelial neoplasia OR prostatic neoplasms):ti,ab,kw 4911

#4 (cancer* OR carcinoma* OR malignan* OR tumor* OR tumour* OR neoplas*):ti,ab,kw 155448

#5 #1 OR #2 OR #3 OR 34 100303

#6 (prostat* AND metastat*):ti,ab,kw 2125

#7 #5 AND #6 1086

#8 MeSH descriptor: [Abiraterone Acetate] explode all trees 95

#9 (abiraterone OR zytiga):ti,ab,kw 444

#10 #8 OR #9 444

#11 #7 AND #10 133

#12 ("randomised controlled trial"):pt 455367

#13 ("controlled clinical trial"):pt 90427

#14 placebo:ti,ab 221369

#15 MeSH descriptor: [] explode all trees and with qualifier(s): [drug therapy - DT] 188680

#16 random*:ti,ab 705808

#17 trial:ti,ab 418505

#18 groups:ti,ab 367003

#19 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 941588

#20 #11 AND #19 110

Appendix 2. MEDLINE search strategy

1. exp Prostatic Neoplasms/
2. exp Prostatic Intraepithelial Neoplasia/
3. (prostatic intraepithelial neoplasia or prostatic neoplasms).tw.
4. (cancer* or carcinoma* or malignan* or tumor* or tumour* or neoplas*).tw.
5. 1 or 2 or 3 or 4
6. (prostat* and metastat*).tw.
7. 5 and 6
8. exp ABIRATERONE ACETATE/
9. (abiraterone or zytiga).tw.
10. 8 or 9
11. 7 and 10

Appendix 3. Embase search strategy

1 exp prostate tumor/

2 exp prostatic intraepithelial neoplasia/

3 (prostatic intraepithelial neoplasia or prostatic neoplasms).tw.

4 (cancer* or carcinoma* or malignan* or tumor* or tumour* or neoplas*).tw.

5 1 or 2 or 3 or 4

6 (prostat* and metastat*).tw.

7 5 and 6

8 exp abiraterone acetate/ or exp abiraterone/

9 (abiraterone or zytiga).tw.

10 8 or 9

11 7 and 10

12 randomized controlled trial.pt.

13 controlled clinical trial.pt.

14 placebo.ti,ab.

15 drug therapy.sh.

16 random*.ti,ab.

17 trial.ti,ab.

18 groups.ti,ab.

19 12 or 13 or 14 or 15 or 16 or 17 or 18

20 11 and 19

Appendix 4. SCOPUS search strategy

TITLE-ABS-KEY ((((prostat* AND intraepithelial AND neoplas*) OR (prostatic AND neoplas*) OR cancer* OR carcinoma* OR malignan* OR tumor* OR tumour* OR neoplas*) AND (prostat* AND metastat*)) AND (abiraterone OR zytiga)) AND (placebo OR random* OR trial OR group)

Appendix 5. Web of Science search strategy

1. TS=(prostat* AND intraepithelial AND neoplas*)

2. TS=(prostatic AND neoplas*)

3. TS=(cancer* OR carcinoma* OR malignan* OR tumor* OR tumour* OR neoplas*)

4. #3 OR #2 OR #1

5. TS=(prostat* AND metastat*)

6. #5 AND #4

7. TS=(abiraterone OR zytiga)

8. TS=(placebo OR random* OR trial OR group)

9. #8 AND #7 AND #6

Appendix 6. LILACS search strategy

(tw:(((prostat* AND intraepithelial AND neoplas*) OR (prostatic AND neoplas*) OR cancer* OR carcinoma* OR malignan* OR tumor* OR tumour* OR neoplas*) AND (prostat* AND metastat*))) AND (tw:((abiraterone OR zytiga))) AND (tw:((placebo OR random* OR trial OR group)))

WHAT'S NEW

Date	Event	Description
15 December 2020	Amended	re-published due to erroneous characters appearing in final published version (known Archie issue)

HISTORY

Protocol first published: Issue 1, 2019

Review first published: Issue 12, 2020

CONTRIBUTIONS OF AUTHORS

Niranjan Sathianathen (NS): wrote the protocol, screened abstracts, reviewed full-text articles, extracted and analyzed data, and drafted the review.

Phillip Dahm (PD): helped to write the protocol and assisted with data interpretation, provided consultation to resolve discrepancies or disagreements, offered clinical expertise, and contributed to drafting of the review.

Sarah Brown (SB): developed search strategy, executed search, contributed review revisions.

Mackinna Oestreich (MO): helped to write the protocol, screened abstracts, reviewed full-text articles, extracted data, and contributed to drafting of the review.

Shilpa Gupta (SG): aided with the data interpretation, provided clinical expertise, contributed to drafting of the review.

Badrinath Konety (BK): aided with the data interpretation, provided clinical expertise, contributed to drafting the review.

Frank Kunath (FK): oversaw protocol development, data interpretation, provided consultation to resolve discrepancies or disagreements, offered clinical expertise, oversaw and revised the final review.

DECLARATIONS OF INTEREST

NS: none known

MO: none known

PD: none known

SB: none known

SG declares the following:

- Stock and other ownership interests: Nektar
- Honoraria: Janssen Oncology, AstraZeneca, Exelixis, Bristol Myers Squibb, Merck Sharp & Dohme, Seattle Genetics, Pfizer
- Speakers' Bureau: Bristol Myers Squibb, Janssen Oncology, Exelixis
- Research funding: Merck, Pfizer, Bristol Myers Squibb, Seattle Genetics

BK declares the following relationships: PhotoCure Inc, FKD Therapeutics, Bristol Myers Squibb, Taris Biomedical, Boston Scientific Group, Merck Inc, Francis Medical

FK: none known

SOURCES OF SUPPORT

Internal sources

- Department of Urology, University of Minnesota, USA

  Partial salary support for Niranjan Sathianathen

External sources

- None, Australia

  N/A

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There was insufficient information in either of the two included trials to analyse time to death due to prostate cancer as a time-to-event outcome, as intended in the protocol, but Fizazi 2017 reported the number of deaths in each group from prostate cancer, and therefore, we analyzed this as a dichotomous outcome in this review. If further information becomes available in future updates, we plan to analyze this outcome using time-to-event methods.

We had also planned to evaluate detection bias separately for objective and subjective outcomes but it was evident that the judgments for outcomes classified as subjective differed among them; therefore we assessed them on an outcome-specific basis to accurately reflect the certainty of evidence.

NOTES

We 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.

Large parts of the background section of this review are based on a previously published protocol and review on alternative immediate taxane-based chemotherapy for metastatic hormone-sensitive prostate cancer (Sathianathen 2017; Sathianathen 2018). This was done with explicit approval of both the review authors and the Cochrane Urology Editorial Group.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Adult; Aged; Aged, 80 and over; Humans; Male; Middle Aged