Hormone-sensitive metastatic prostate cancer: docetaxel

Evidence summary
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www.nice.org.uk/guidance/esuom50

Key points from the evidence

The content of this evidence summary was up-to-date in January 2016. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

Randomised controlled trial (RCT) data suggest that docetaxel improves overall survival and time to disease progression in men with hormone-sensitive metastatic prostate cancer. Two RCTs found that, compared with androgen deprivation therapy (ADT) alone, docetaxel combined with ADT statistically significantly improved overall survival by around 10–15 months in this population. No statistically significant difference was seen between the groups in another, smaller RCT. Time to disease progression was statistically significantly longer with docetaxel plus ADT compared with ADT alone in all 3 RCTs. These findings are reinforced by a meta-analysis of the RCTs.

The toxicity of docetaxel is well-established. Nevertheless, most participants in the RCTs tolerated the planned number of docetaxel treatment cycles.

Regulatory status: Docetaxel is licensed for treating men with hormone-resistant metastatic
prostate cancer. Use of docetaxel for treating men with hormone-sensitive metastatic prostate cancer is off-label.
### Effectiveness

In open-label RCTs in men with hormone-sensitive prostate cancer, compared with ADT alone, docetaxel plus ADT statistically significantly improved overall survival:

- by 10 months in men with metastatic or non-metastatic disease in **STAMPEDE** (n=1776, median follow-up: 43 months, p=0.006)

- by 15 months in a subgroup of men with metastases in **STAMPEDE** (n=1086, median follow-up: 43 months, p=0.005)

- by 13.6 months in men with metastases in **CHAARTED** (n=790, median follow-up: 29 months, p<0.001)

- no statistically significant difference was seen between the groups in a smaller RCT **GETUG-AFU 15**, although overall survival was 4.7 months longer with docetaxel (n=385, median follow-up: 50 months).

In men with hormone-sensitive metastatic prostate cancer at 4 years, estimates based on a meta-analysis of the 3 RCTs (**STOpCaP**, n=2992) found:

- a 9% absolute improvement in overall survival with docetaxel compared with ADT alone (49% compared with 40%, p<0.0001, number needed to treat [NNT] 12)

### Safety

- Four deaths in **GETUG-AFU 15**, 1 death in **CHAARTED** and 8 deaths in **STAMPEDE** (1 with docetaxel plus ADT and 7 with docetaxel, zoledronic acid and ADT) were considered possibly or probably related to docetaxel treatment.

- In men taking docetaxel plus ADT, severe, life-threatening or disabling adverse events or death (grade 3–5 adverse events) were reported in 38.1% of men in **GETUG-AFU 15**, 29.5% of men in **CHAARTED** and 52.4% of men in **STAMPEDE**. 32.5% of men taking ADT alone in **STAMPEDE** reported grade 3–5 adverse events.

- According to the **summary of product characteristics**, the adverse effects most commonly reported with docetaxel 75 mg/m² when used for prostate cancer are neutropenia (32%), anaemia (4.9%), fatigue (3.9%) and infection (3.3%).
• a 16% absolute improvement in time to disease progression with docetaxel compared with ADT alone (treatment failure 64% compared with 80%, p<0.0001, NNT 7).

<table>
<thead>
<tr>
<th>Patient factors</th>
<th>Resource implications</th>
</tr>
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<tbody>
<tr>
<td>In STAMPEDE and GETUG-AFU 15 respectively, 13.1% and 20.6% of men taking docetaxel plus ADT discontinued treatment due to adverse events. This outcome was not reported in CHAARTED.</td>
<td>• Docetaxel concentrate for solution for infusion costs £162.75 for 0.5 ml and £534.75 for 2 ml of the 40 mg/ml strength (MIMS, December 2015).</td>
</tr>
<tr>
<td>In the 3 RCTs, half to three quarters of men tolerated the study dosage of docetaxel for the planned treatment duration (75 mg/m² 3-weekly, usually for 6 cycles). However, the toxicity of docetaxel means some men (particularly those with poor performance status or comorbidities) may prefer other treatment options.</td>
<td>• The cost of 6 cycles of docetaxel 75 mg/m² 3-weekly is approximately £6138 per person (see below).</td>
</tr>
<tr>
<td>Little information is available on quality of life. GETUG-AFU 15 reported that, although quality of life was statistically significantly impaired during docetaxel treatment, global scores were generally similar between the combination and ADT alone groups at 12 months.</td>
<td>• These are the costs of docetaxel only (excluding VAT) and do not include any procurement discounts or other costs incurred, such as dilution and administration, or the cost of standard supportive therapy.</td>
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</table>

**Introduction and current guidance**

Prostate cancer is the most common cancer in men. Over 40,000 cases were registered in 2013, accounting for 27% of new cancers in males. Up to 25% of men diagnosed with prostate cancer present with metastases. The average 5-year survival rate for men with metastatic prostate cancer is 30%; 10% will survive for at least 10 years.
The androgen receptor is involved in the growth and spread of prostate cancer. Prostate cancer can, therefore, be treated hormonally using androgen deprivation therapy (ADT). This includes surgical castration (bilateral orchidectomy) and medical castration (usually with luteinising-hormone-releasing hormone [LHRH] agonists, also known as gonadotropin-releasing hormone [GnRH] agonists or analogues). As a prostate cancer progresses, further genetic mutations can affect the androgen receptors and allow increasing numbers to function without androgen. ADT then becomes less effective. This is known as hormone-resistant (castration-resistant, hormone-relapsed or hormone-refractory) prostate cancer.

For men with hormone-sensitive metastatic prostate cancer, the NICE guideline on prostate cancer recommends bilateral orchidectomy or continuous LHRH agonist therapy, anti-androgen therapy with bicalutamide (in men who are willing to accept the adverse effects; off-label) or combined androgen blockade (not first-line).

NICE recommends docetaxel as a possible treatment for men with hormone-resistant metastatic prostate cancer if the man is well enough to care for himself with occasional assistance. This evidence summary considers the efficacy and safety of docetaxel (in combination with ADT) for treating men with hormone-sensitive prostate cancer.

Full text of introduction and current guidance.

**Product overview**

Docetaxel is an antineoplastic agent in the taxane class. As well as other non-prostate cancer indications, docetaxel (in combination with prednisone or prednisolone) is licensed for treating men with hormone-resistant metastatic prostate cancer (see the summary of product characteristics for Taxotere).

Use of docetaxel for treating men with hormone-sensitive metastatic prostate cancer is off-label.

Full text of product overview.
Evidence review

• This evidence review includes 3 open-label randomised controlled trials (RCTs) that compared the effects of docetaxel in combination with ADT with ADT alone in men with hormone-sensitive prostate cancer. GETUG-AFU 15 and CHAARTED included only men with metastases: in STAMPEDE, 61% of men had metastases. A meta-analysis (STOpCaP) on docetaxel for men with hormone-sensitive metastatic and non-metastatic prostate cancer, which includes the 3 RCTs, is also outlined. In STOpCaP, analyses for docetaxel also include men from another treatment group in STAMPEDE who received a treatment regimen of docetaxel, zoledronic acid and ADT (which was not found to improve overall survival statistically significantly better than docetaxel plus ADT and is not discussed in any detail in this evidence summary).

• STAMPEDE and CHAARTED found that docetaxel (75 mg/m² 3-weekly for 6 cycles) combined with ADT statistically significantly improved overall survival compared with ADT alone in men with hormone-sensitive metastatic prostate cancer. However, no statistically significant difference was seen between the groups in GETUG-AFU 15 (docetaxel 75 mg/m² 3-weekly, median 8 cycles).

• In STAMPEDE, in the docetaxel plus ADT group compared with the ADT alone group, median overall survival was 10 months longer in the total population of men with and without metastases (n=1776; 81 months compared with 71 months; hazard ratio [HR] 0.78, 95% confidence interval [CI] 0.66 to 0.93, p=0.006) and 15 months longer in the subgroup of men with metastases (n=1086; 60 months compared with 45 months; HR 0.76, 95% CI 0.62 to 0.92, p=0.005). In men using docetaxel plus ADT compared with ADT alone, median overall survival was 13.6 months longer in CHAARTED (n=790; 57.6 months compared with 44.0 months; HR 0.61, 95% CI 0.47 to 0.80, p<0.001) and 4.7 months longer in GETUG-AFU 15 (n=385; 58.9 months compared with 54.2 months; p=0.955). In GETUG-AFU 15, the authors suggest that overall survival may not have reached statistical significance because of insufficient statistical power or confounding caused by crossover use of docetaxel in the ADT alone group when prostate cancer became hormone-resistant. A meta-analysis of men with metastatic prostate cancer (3 RCTs [STAMPEDE, CHAARTED and GETUG-AFU 15], n=2992) in STOpCaP found overall survival was statistically significantly increased at 4 years in the docetaxel group compared with the ADT alone group (estimated overall survival 49% compared with 40% respectively; HR 0.77, 95% CI 0.68 to 0.87, p<0.0001; number needed to treat [NNT] 12).
• **CHAARTED** and **GETUG-AFU 15** found that treatment with docetaxel and ADT statistically significantly improved median time to clinical progression (including death and clinical signs and symptoms of worsening disease) compared with ADT alone (33.0 months compared with 19.8 months; HR 0.61, 95% CI 0.50 to 0.75, p<0.001 and 23.5 months compared with 15.4 months; HR 0.75, 95% CI 0.59 to 0.94, p=0.015 respectively). Median time to biochemical progression (including death, clinical progression and deterioration in biological markers) was statistically significantly improved with docetaxel plus ADT compared with ADT alone in **STAMPEDE** (total population: 37 months compared with 20 months; HR 0.61, 95% CI 0.53 to 0.70, p<0.0001 and metastatic population: months to progression not reported; HR 0.61, 95% CI 0.53 to 0.71, p<0.0001) and **GETUG-AFU 15** (22.9 months compared with 12.9 months; HR 0.72, 95% CI 0.57 to 0.91, p=0.005). The **STOpCaP** meta-analysis found that, in men with metastatic prostate cancer at 4 years, time to disease progression was statistically significantly longer in men taking docetaxel plus ADT compared with ADT alone (estimated treatment failure 64% compared with 80%; HR 0.64, 95% CI 0.58 to 0.70, p<0.0001; NNT 7).

- There is currently no evidence that the effect of docetaxel varies significantly in subgroups of men with hormone-sensitive prostate cancer. The **STOpCaP** meta-analysis found that, in men with metastases, overall survival was statistically significantly increased at 4 years with docetaxel compared with ADT alone, but there was no significant difference between the groups in men with non-metastatic prostate cancer. However, the smaller number of deaths in men without metastases means this analysis was probably underpowered to detect a difference between the groups when it was undertaken, but it is possible that the results may change with longer follow-up. The meta-analysis found that time to disease progression was statistically significantly longer in men taking docetaxel compared with ADT alone in subgroups of men both with and without metastatic prostate cancer.

- Little information is available on the effect of these regimens on quality of life. **GETUG-AFU 15** reported that, although quality of life was statistically significantly impaired during docetaxel treatment, global scores were generally similar between the combination and ADT alone groups at 12 months. **STAMPEDE** is expected to report on patient-reported outcomes in due course.
• There are differences between the RCTs that make it difficult to compare the results; for example, the numbers of men with high volume compared with low volume metastases, the proportions of men with metastatic disease at diagnosis or following treatment for localised disease, definitions of outcomes, use of newer treatments for prostate cancer, and the length of follow-up. The number of men with metastases at diagnosis was high in all 3 RCTs (60–70% compared with 25% in the general population). The evidence for using docetaxel in men with non-metastatic or recurrent metastatic hormone-sensitive prostate cancer is less robust.

• In STAMPEDE and CHAARTED, 77% and 74% of men respectively received the planned 6 cycles of docetaxel. In GETUG-AFU 15, 48% of men received the maximum 9 cycles of treatment: the median number of cycles was 8. This suggests that treatment was tolerated.

• Four deaths in GETUG-AFU 15, 1 death in CHAARTED and 8 deaths in STAMPEDE (7 in the docetaxel, zoledronic acid and ADT arm and 1 in the docetaxel plus ADT arm) were considered possibly or probably related to docetaxel treatment. Grade 3–5 adverse events (severe, life-threatening or disabling adverse events or those resulting in death) were reported in 38.1% of men taking docetaxel plus ADT in GETUG-AFU 15 (72/189 compared with 0/1228 with ADT alone), 29.5% of men in CHAARTED (115/390; results for ADT alone not reported) and 52.4% of men in STAMPEDE (288/550 compared with 399/1288 [32.5%] with ADT alone). Statistical analyses were not reported.

• According to the summary of product characteristics for Taxotere, the originator brand of docetaxel, the adverse effects most commonly reported with docetaxel 75 mg/m² when used for prostate cancer (in combination with prednisone or prednisolone) are neutropenia (32%), anaemia (4.9%), fatigue (3.9%), infection (3.3%), nausea (2.4%), vomiting (1.2%), diarrhoea (1.2%) and peripheral sensory neuropathy (1.2%).

• Although the adverse event profile of docetaxel is well-established, caution should be used in men with comorbidity and poor performance status (who were generally excluded from the RCTs), and men should be monitored carefully for toxicity.

Full text of evidence review.

Context and estimated impact for the NHS

In the 3 RCTs included in this evidence summary, docetaxel 75 mg/m² was administered every 3 weeks, usually for 6 cycles. Assuming the average body surface area of a man with cancer is 1.91 m² (Sacco et al. 2010), the approximate dose of docetaxel is 140 mg, which costs £1023 if 1 x 2 ml vial plus 3 x 0.5 ml vials containing 40 mg/ml are used. The cost of 6 cycles of docetaxel treatment is, therefore, approximately £6138 per person (MIMS, November 2015).
This is the cost of docetaxel only (excluding VAT) and does not include any procurement discounts or other costs incurred, such as dilution and administration or standard supportive therapy.

Full text of context and estimated impact for the NHS.

About this evidence summary

‘Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, but this summary is not NICE guidance.

Full evidence summary

Introduction and current guidance

Prostate cancer is the most common cancer in men. Over 40,000 cases were registered in 2013, accounting for 27% of new cancers in males. The age-standardised cancer incidence rate for prostate cancer was 186 cases per 100,000 males in that year, a rise of 6.3% since 2004 (Office for National Statistics, Cancer registration statistics, England, 2013).

Most prostate cancers are relatively benign and grow slowly; a minority are aggressive in their tendency to invade local structures or to metastasise to remote tissues. Localised prostate cancer usually develops in the outer zone of the prostate, where it seldom causes symptoms. Locally advanced prostate cancer extends beyond the capsule of the prostate and is often asymptomatic when diagnosed. Metastatic prostate cancer most commonly spreads to the bones, where it can cause pain, pathological fractures or spinal cord compression. Up to 25% of men diagnosed with prostate cancer present with metastases (NICE clinical knowledge summary, prostate cancer).

The prognosis for men with prostate cancer varies according to clinical and pathological features,
and the prognostic risk can be grouped according the prostate-specific antigen (PSA) level, Tumour node metastasis (TNM) stage, and Gleason score (see the NICE guideline on prostate cancer for more information). Men presenting with metastatic prostate cancer have an average 5-year survival rate of 30%; 10% will survive for at least 10 years (NICE clinical knowledge summary, prostate cancer).

According to the NICE guideline on prostate cancer, and depending on the stage and prognostic risk of the person's disease, treatment options for prostate cancer include:

- watchful waiting and active surveillance
- radical prostatectomy
- radical external beam radiotherapy, brachytherapy or pelvic radiotherapy,
- androgen deprivation therapy (ADT) and
- chemotherapy.

The androgen receptor is involved in the growth and spread of prostate cancer. Prostate cancer can, therefore, be treated hormonally using ADT. This includes surgical castration (bilateral orchidectomy) and medical castration using luteinising-hormone-releasing hormone [LHRH] agonists, such as buserelin, goserelin, leuprorelin and triptorelin (also known as gonadotropin-releasing hormone [GnRH] agonists or analogues), and LHRH antagonists, such as degarelix (a NICE technology appraisal on degarelix is in development). As a prostate cancer progresses, further genetic mutations can affect the androgen receptors and allow increasing numbers to function without androgen. ADT then becomes less effective (NICE clinical knowledge summary, prostate cancer). This is known as hormone-resistant (castration-resistant, hormone-relapsed or hormone-refractory) prostate cancer.

Cyproterone acetate, flutamide and bicalutamide are anti-androgens that inhibit the tumour ‘flare’ that can occur when LHRH agonists are initiated. Cyproterone acetate and flutamide are also licensed for use alone in men with hormone-resistant metastatic prostate cancer. Bicalutamide is used for prostate cancer either alone or as an adjunct to other therapy, according to the clinical circumstances. Abiraterone and enzalutamide are newer anti-androgens, which are licensed for treating men with hormone-resistant metastatic prostate cancer in some circumstances (British national formulary, December 2015; also see the NICE guidance on enzalutamide and abiraterone).

For men with hormone-sensitive metastatic prostate cancer, the NICE guideline on prostate cancer recommends bilateral orchidectomy or continuous LHRH agonist therapy, anti-androgen therapy
with bicalutamide (in men who are willing to accept the adverse effects; off-label) or combined androgen blockade (not first-line).

NICE technology appraisal guidance recommends docetaxel as a possible treatment for men with hormone-resistant metastatic prostate cancer if the man is well enough to care for himself with occasional assistance. Treatment should be stopped at the end of a planned course of up to 10 cycles of docetaxel. It should be stopped early if the man experiences serious adverse effects, or if the disease is getting worse. NICE does not recommend using docetaxel again if the disease comes back after the first course of treatment has finished.

This evidence summary considers the efficacy and safety of docetaxel (in combination with ADT) for treating men with metastatic hormone-sensitive prostate cancer, before the cancer becomes hormone-resistant, because questions have been raised over whether chemotherapy can improve survival if it is administered before the disease progresses.

Product overview

Drug action

Docetaxel is an antineoplasic agent in the taxane class. It works by disrupting the microtubular network that is essential for mitotic and interphase cellular functions, causing inhibition of cell division and cell death (Docetaxel for the treatment of hormone-refractory metastatic prostate cancer, NICE technology appraisal 101).

Regulatory status

As well as other non-prostate cancer indications, docetaxel (in combination with prednisone or prednisolone) is licensed for treating men with hormone-resistant metastatic prostate cancer (see the summary of product characteristics for Taxotere). Use of docetaxel for treating men with hormone-sensitive metastatic prostate cancer is off-label.

In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using docetaxel outside its authorised indications.

Docetaxel is administered as a 1-hour infusion once every 3 weeks. The recommended dose for hormone-resistant metastatic prostate cancer is 75 mg/m², with twice daily oral administration of prednisone or prednisolone at a dose of 5 mg (see the summary of product characteristics for Taxotere).
Cost

The originator brand of docetaxel is now off-patent in the UK and several generic products are available. Docetaxel concentrate for solution for infusion ([MIMS](https://www.mims.co.uk), December 2015) costs:

- £162.75 for 2 ml, £534.75 for 8 ml and £1069.50 for 16 ml of the 10 mg/ml strength
- £160.00 for 2 ml, £530.00 for 4 ml and £900.00 for 7 ml of the 20 mg/ml strength
- £162.75 for 0.5 ml and £534.75 for 2 ml of the 40 mg/ml strength.

Costs may vary depending on local procurement arrangements.

Evidence review

This evidence review includes 3 randomised controlled trials (RCTs) that compared the effects of docetaxel in combination with ADT with ADT alone in men with hormone-sensitive prostate cancer. Two of the RCTs ([GETUG-AFU 15](https://www.getug-afu15.org), n=385 and [CHAARTED](https://chaarted.nhs.uk), n=790) enrolled men with metastatic prostate cancer. The third ([STAMPEDE](https://www.stroke.nhs.uk/stampe-de), n=2962) enrolled men with metastatic, high-risk locally advanced or recurrent prostate cancer. STAMPEDE included 2 arms assessing zoledronic acid plus ADT with or without docetaxel, which are not discussed in any detail in this evidence summary. The study designs and methods, and the baseline characteristics of the participants in the 3 RCTs are outlined in table 1. The results of the RCTs are listed in table 2.

A systematic review and meta-analysis (part of the Systemic treatment options for prostate cancer [STOpCaP](https://www.stroke.nhs.uk/stampe-de) project) has considered the evidence for adding docetaxel (or bisphosphonates) to ADT (standard of care) in men with hormone-sensitive prostate cancer. The investigators identified 14 eligible RCTs for inclusion, including the 3 RCTs discussed in this evidence summary. Men with and without metastatic disease were assessed separately. The outcomes considered were overall survival (time from randomisation until death from any cause) and failure-free survival (time to biochemical failure, clinical failure [local relapse or metastases] or death from any cause). In this evidence summary failure-free survival is reported as time to disease progression for consistency between the studies. Analyses for docetaxel also included men who were receiving a treatment regimen of docetaxel, zoledronic acid and ADT in another arm of the STAMPEDE study.

The STOpCaP analysis for men with metastatic prostate cancer identified 5 RCTs ([GETUG-AFU 15](https://www.getug-afu15.org), [CHAARTED](https://chaarted.nhs.uk), [STAMPEDE](https://www.stroke.nhs.uk/stampe-de), 1 yet to report suitable data and 1 ongoing), 3 of which ([GETUG-AFU 15](https://www.getug-afu15.org), [CHAARTED](https://chaarted.nhs.uk) and [STAMPEDE](https://www.stroke.nhs.uk/stampe-de)) reported the outcomes of interest (n=2992). The RCTs used docetaxel 75 mg/m² every 3 weeks for 6 or 9 cycles for a median of 29 to 82.9 months. The median
The age of the participants was 63–66 years and the majority had good performance status. The included RCTs were assessed as being at low risk of bias.

The analysis for men with non-metastatic prostate cancer identified 11 RCTs (including STAMPEDE, 7 yet to report suitable data), 4 of which reported the outcomes of interest (n=2348; STAMPEDE, GETUG 12, RTOG 0521 and TAX-3501). Three of the RCTs used docetaxel 75 mg/m² every 3 weeks for 6 cycles and the other used 70 mg/m² per cycle plus estramustine. The median age of the men was 62–66 years. Median follow-up was 39 to 90 months. The included RCTs were assessed as being at low risk of bias.

The results of the meta-analysis are discussed in the clinical effectiveness section of this evidence summary, along with the results of the 3 key RCTs.

Table 1 Summary of design, methods and participants for GETUG-AFU 15, CHAARTED and STAMPEDE

<table>
<thead>
<tr>
<th>Study design</th>
<th>GETUG-AFU 15</th>
<th>CHAARTED</th>
<th>STAMPEDE</th>
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<tbody>
<tr>
<td></td>
<td>Open-label RCT. 29 centres in France and 1 in Belgium.</td>
<td>Open-label RCT. In the USA (number of centres not reported).</td>
<td>Open-label RCT. Over 100 UK and Swiss centres.</td>
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### Participants

| 385 men with confirmed metastatic prostate cancer, a Karnofsky score\(^a\) of ≥70%, a life expectancy of ≥3 months and adequate hepatic, haematological and renal function. Men who had taken previous chemotherapy for metastatic disease were excluded, as were those who had surgical castration before metastatic disease occurred. |
| 790 men with confirmed metastatic prostate cancer or raised PSA, radiologic evidence of metastatic disease, an ECOG score\(^b\) of 0–2. Organ function had to be adequate for docetaxel treatment. |
| 2962 men with prostate cancer newly diagnosed as metastatic, node-positive or high-risk locally advanced, or previously treated with radical surgery and/or radiotherapy and now relapsing with high-risk features. Long-term ADT was intended for all participants, who had to be fit for chemotherapy with no significant cardiovascular history. WHO performance status was 0–2. |

### Baseline characteristics

| Balanced between the groups. |
| Balanced between the groups. |
| Balanced between the groups. |

| Median age: 63–64 years. |
| Median age: 63–64 years. |
| Median age: 65 years. |

| Mean Karnofsky score: 100%. |
| ECOG score of 0: 70%. |
| Gleason score\(^c\) ≥8: 57%. |
| Gleason score\(^c\) ≥8: 60%. |
| Node-positive: 54%. |
| High-volume disease\(^d\): 65%. |
| Metastatic at diagnosis: 71%. |
| No prior curative therapy: 73%. |
| Newy diagnosed: 94%, with 62% metastatic. |
| Recurrent disease: 6%, with 48% metastatic. |
### Conditions for allowing ADT

<table>
<thead>
<tr>
<th>Conditions for allowing ADT</th>
<th>Previous treatment if discontinued ≥12 months before study inclusion. For metastatic disease if started ≤2 months before randomisation.</th>
<th>Adjuvant therapy if duration ≤24 months, with progression &gt;12 months after completing therapy. For metastatic disease if started &lt;120 days before randomisation and no evidence of progression.</th>
<th>Not applicable. All participants were commencing first-line long-term ADT.</th>
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### ADT

<table>
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<tr>
<th>ADT</th>
<th>ADT was started 15–60 days before enrolment in 50% of participants.</th>
<th>Median pre-study duration 1.2–1.3 months. No ADT before randomisation 13%.</th>
<th>ADT was started a median of 2 weeks before randomisation and 9 weeks before docetaxel.</th>
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</table>

### Intervention and comparison

<table>
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<tr>
<th>Intervention and comparison</th>
<th>1:1 to ADT alone (n=193) or ADT plus docetaxel 75 mg/m² 3-weekly for up to 9 cycles (median 8 cycles; n=192). An oral corticosteroid was given on the days before, of and after docetaxel treatment. Bisphosphonate treatment was allowed.</th>
<th>1:1 to ADT alone (n=393) or ADT plus docetaxel 75 mg/m² 3-weekly for 6 cycles (n=397). Oral dexamethasone was taken 12 hours, 3 hours and 1 hour before docetaxel. Calcium and vitamin D was also taken. Zoledronic acid and denosumab were allowed, as were growth factors (G-CSF).</th>
<th>2:1:1:1 to ADT alone (n=1184), ADT plus docetaxel 75 mg/m² 3-weekly for 6 cycles (n=592), ADT plus zoledronic acid 4 mg 3-weekly for 6 cycles then 4-weekly to 2 years (n=593), and ADT plus docetaxel and zoledronic acid (n=593). Radiotherapy was considered in certain clinical circumstances (28–29% across arms). Prednisolone 10 mg was taken before docetaxel, with standard premedication. No recommendations were made around use of G-CSF with docetaxel.</th>
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<tbody>
<tr>
<td>Outcomes</td>
<td>Primary outcome: overall survival. Selected secondary outcomes: time to clinical progression, time to biochemical progression, median time to subsequent treatment, adverse events.</td>
<td>Primary outcome: overall survival. Selected secondary outcomes: time to clinical progression, adverse events.</td>
<td>Primary outcome: overall survival. Selected secondary outcomes: time to treatment failure, adverse events.</td>
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<td>Follow-up</td>
<td>3-weekly during docetaxel treatment, otherwise 3-monthly. Median follow-up: 50 months. No men were lost to follow-up.</td>
<td>3-weekly during docetaxel treatment, otherwise 3-monthly. Published data available for 84 months. Median follow-up: 29 months. 3 men were lost to follow-up.</td>
<td>6-weekly to 6 months, 12-weekly to 2 years, 6-monthly to 5-years, then annually. Median follow-up: 43 months. No men were lost to follow-up.</td>
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<tr>
<td>Analysis</td>
<td>Efficacy analyses were by intention-to-treat. Safety analyses included all men who received treatment.</td>
<td>Efficacy analyses were by intention-to-treat. Safety analyses included all men who received docetaxel and had follow-up data. Adverse events due to ADT were not routinely recorded.</td>
<td>Efficacy analyses were by intention-to-treat. Safety analyses included all men with at least 1 assessment of adverse events.</td>
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</table>
Abbreviations: ADT, androgen deprivation therapy (orchidectomy or luteinising-hormone-releasing hormone [LHRH] agonists alone and/or anti-androgens); ECOG, Eastern Cooperative Oncology Group performance-status score; G-CSF, granulocyte colony stimulating factor; PSA, prostate specific antigen; RCT, randomised controlled trial; USA, United States of America; WHO, World Health Organisation.

a On a scale of 0–100, with a higher score indicating better ability to perform activities of daily living.
b On a scale of 0–5, with higher scores indicating greater disability. Men with a score of 2 were eligible if the reduced function was due to prostate cancer.
c On a scale of 2–10, with higher scores indicating a more aggressive form of prostate cancer and a worse prognosis.
d Presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis.
e Therapy given after radical treatment with surgery or radiotherapy.
f Time from randomisation until death from any cause.
g Time to death or clinical progression (progression of pre-existing lesions using RECIST, occurrence of new bone lesions or, in men with only bone lesions, new soft tissue lesions).
h Time to death, PSA progression (decrease of ≥50% plus other criteria showing deterioration) or clinical progression.
i Time until increasing symptoms of bone metastases.
j Time until death from prostate cancer, biochemical failure (according to specified criteria showing deterioration in PSA; James ND et al. 2015), or progression locally, in lymph nodes or in distant metastases.
k All randomly assigned men regardless of eligibility and treatment status.

Table 2 Summary of results for GETUG-AFU 15, CHAARTED and STAMPEDE

<table>
<thead>
<tr>
<th>Randomised</th>
<th>ADT plus docetaxel</th>
<th>ADT alone</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>GETUG-AFU 15</td>
<td>n=192</td>
<td>n=193</td>
<td></td>
</tr>
<tr>
<td>CHAARTED</td>
<td>n=397</td>
<td>n=393</td>
<td></td>
</tr>
<tr>
<td>STAMPEDE</td>
<td>n=592</td>
<td>n=1184</td>
<td></td>
</tr>
</tbody>
</table>
### Efficacy

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Median Survival (95% CI)</th>
<th>Median Survival (95% CI)</th>
<th>Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GETUG-AFU 15</td>
<td>n=192</td>
<td>58.9 months (50.8 months to 69.1 months)</td>
<td>54.2 months (42.2 months to not reached)</td>
<td>4.7 months</td>
<td>Not statistically significant (HR 1.01, 95% CI 0.75 to 1.36)</td>
</tr>
<tr>
<td>CHAARTED</td>
<td>n=397</td>
<td>57.6 months (95% CI not reported)</td>
<td>44.0 months (95% CI not reported)</td>
<td>Difference 13.6 months. Statistically significantly longer in the docetaxel group. (HR 0.61, 95% CI 0.47 to 0.80).</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>STAMPEDE total</td>
<td>n=592</td>
<td>81 months (95% CI not reported)</td>
<td>71 months (95% CI not reported)</td>
<td>Difference 10 months. Statistically significantly longer in the docetaxel group. (HR 0.78, 95% CI 0.66 to 0.93).</td>
<td>p=0.006</td>
</tr>
<tr>
<td>metastatic and non-metastatic population</td>
<td>n=1184</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAMPEDE metastatic subgroup only</td>
<td>n=362</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total population</td>
<td>n=1184</td>
<td>81 months (95% CI not reported)</td>
<td>71 months (95% CI not reported)</td>
<td>Difference 10 months. Statistically significantly longer in the docetaxel group. (HR 0.78, 95% CI 0.66 to 0.93).</td>
<td>p=0.006</td>
</tr>
</tbody>
</table>
### STAMPEDE: metastatic subgroup only

<table>
<thead>
<tr>
<th></th>
<th>60 months (95% CI not reported)</th>
<th>45 months (95% CI not reported)</th>
<th>Difference 15 months. Statistically significantly longer in the docetaxel group. HR 0.76, 95% CI 0.62 to 0.92. p=0.005.</th>
</tr>
</thead>
</table>

### Selected secondary outcomes:

**Overall survival in men with high-volume disease only (median)**

<table>
<thead>
<tr>
<th></th>
<th>CHAARTED(^b) 49.2 months (95% CI not reported)</th>
<th>32.2 months (95% CI not reported)</th>
<th>Difference 17.0 months. Statistically significantly longer in the docetaxel group. HR 0.60 (95% CI 0.45 to 0.81). p&lt;0.001.</th>
</tr>
</thead>
</table>

**Time to clinical progression (median)**

<table>
<thead>
<tr>
<th></th>
<th>GETUG-AFU 15(^c) 23.5 months (95% CI 20.5 months to 31.9 months)</th>
<th>15.4 months (95% CI 12.5 months to 19.8 months)</th>
<th>Difference 8.1 months. Statistically significantly longer in the docetaxel group. HR 0.75 (95% CI 0.59 to 0.94). p=0.015.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Time to biochemical progression (median)</td>
<td>CHAARTED&lt;sup&gt;d&lt;/sup&gt;</td>
<td>GETUG-AFU 15&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------------------------------------</td>
<td>-----------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33.0 months (95% CI 27.3 months to 41.2 months)</td>
<td>19.8 months (95% CI 17.9 months to 22.8 months)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19.8 months (95% CI 17.9 months to 22.8 months)</td>
<td>Difference 13.2 months.</td>
</tr>
<tr>
<td>Safety</td>
<td>GETUG-AFU 15</td>
<td>N=189&lt;sup&gt;g&lt;/sup&gt;</td>
<td>n=186&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>--------</td>
<td>--------------</td>
<td>------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>CHAARTED</td>
<td>N=390&lt;sup&gt;i&lt;/sup&gt;</td>
<td>392&lt;sup&gt;j&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>STAMPEDE&lt;sup&gt;k&lt;/sup&gt;: total population</td>
<td>n=550</td>
<td>n=1228</td>
<td></td>
</tr>
</tbody>
</table>

**Patients reporting grade 3-5 adverse events<sup>l</sup>**

| GETUG-AFU 15 | 38.1% (72/189) | None | No statistical analysis reported |
| CHAARTED | 29.5% (115/390) | Not reported<sup>l</sup> | Not applicable |
| STAMPEDE | 52.4% (288/550) | 32.5% (399/1228) | No statistical analysis reported |

**Patients discontinuing treatment due to adverse events**

| GETUG-AFU 15 | 20.6% (39/189) | Not reported | Not applicable |
| CHAARTED | Not reported | Not reported |
| STAMPEDE | 13.1% (72/550) | Not reported | Not applicable |

**Patients experiencing grade 3–5 neutropenia**

<p>| GETUG-AFU 15&lt;sup&gt;m&lt;/sup&gt; | 32.3% (61/189) | None | No statistical analysis reported |
| CHAARTED | 12.1% (47/390) | Not reported&lt;sup&gt;l&lt;/sup&gt; | Not applicable |</p>
<table>
<thead>
<tr>
<th>Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; RECIST, Response Evaluation Criteria in Solid Tumours.</th>
<th>STAMPEDE</th>
<th>12.0% (66/550)</th>
<th>0.5% (6/1228)</th>
<th>No statistical analysis reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Time from randomisation until death from any cause.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>Presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis. Median survival not reached in men with low volume disease.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>c</td>
<td>Time to death or clinical progression (progression of pre-existing lesions using RECIST, occurrence of new bone lesions or, in men with only bone lesions, new soft tissue lesions).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>Time until increasing symptoms of bone metastases.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e</td>
<td>Time to death, PSA progression (decrease of ≥50% plus other criteria showing deterioration) or clinical progression.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f</td>
<td>Time until death from prostate cancer, biochemical failure (according to specified criteria showing deterioration in PSA; James ND et al. 2015), or progression locally, in lymph nodes or in distant metastases, reported as time to treatment failure.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g</td>
<td>4 men did not receive docetaxel because consent was withdrawn. Number includes 1 person from the ADT group who received docetaxel.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>h</td>
<td>3 men did not receive ADT because consent was withdrawn. Number excludes 3 men who did not have safety assessment, 2 early deaths and 1 unknown.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i</td>
<td>7 men did not start treatment, including 5 who withdrew consent, 1 medical decision and 1 lack of information.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>j</td>
<td>Adverse events due to ADT were not routinely recorded.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>k</td>
<td>About 8% of men in the docetaxel group and 12% of men in the zoledronic acid plus docetaxel group did not start docetaxel treatment and were analysed in the ADT only group. Similar results were obtained in the intention-to-treat population.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>l</td>
<td>For example, severe adverse events that result in death or are life threatening, result in hospital admission or extension of hospital stay or cause permanent disability or temporary incapacity (Common terminology criteria for adverse events).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>m</td>
<td>Part way through the study, the independent data monitoring committee recommended granulocyte colony stimulating factor after docetaxel to manage neutropenia.</td>
<td></td>
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</tr>
</tbody>
</table>
Clinical effectiveness

Overall survival in the individual RCTs

STAMPEDE (n=1086) and CHAARTED (n=790) found that docetaxel (75 mg/m$^2$ 3-weekly for 6 cycles) combined with ADT statistically significantly improved overall survival compared with ADT alone in men with hormone-sensitive metastatic prostate cancer. However, no statistically significant difference was seen between the groups in GETUG-AFU 15 (n=385; docetaxel 75 mg/m$^2$ 3-weekly, median 8 cycles).

STAMPEDE (n=1776) included men with newly diagnosed (94%, with 62% metastatic and 38% node positive or high-risk locally advanced) or recurrent prostate cancer (6%, with 48% metastatic) who were starting long-term ADT. After a median follow-up of 43 months, overall survival was 10 months longer in the docetaxel plus ADT group compared with the ADT alone group (median 81 months compared with 71 months, and 5-year survival 63% compared with 55% respectively; hazard ratio [HR] 0.78, 95% confidence interval [CI] 0.66 to 0.93, p=0.006).

In a pre-planned subgroup analysis in men with metastatic prostate cancer (n=1086), overall survival was statistically significantly improved by 15 months in the docetaxel plus ADT group compared with the ADT alone group (median 60 months compared with 45 months, and 5-year survival 50% compared with 39% respectively; HR 0.76, 95% CI 0.62 to 0.92, p=0.005).

Compared with ADT alone, overall survival was also statistically significantly improved in men taking docetaxel, zoledronic acid and ADT (n=1777; total population: median 76 months compared with 71 months; HR 0.82, 95% CI 0.69 to 0.97, p=0.022) but not in men taking zoledronic acid and ADT (p=0.450). Adding zoledronic acid to docetaxel did not appear to add any statistically significant advantage in men with or without metastatic prostate cancer (n=1777; p=0.592).

In CHAARTED, after a median follow-up of 28.9 months, overall survival was 13.6 months longer in men with confirmed metastatic prostate cancer taking docetaxel plus ADT, compared with men taking ADT alone (median 57.6 months compared with 44.0 months respectively; HR 0.61, 95% CI 0.47 to 0.80, p<0.001).

After a median follow-up of 50 months, median survival in GETUG-AFU 15 was 4.7 months longer in men with metastatic prostate cancer who were taking docetaxel plus ADT than in men taking ADT alone but the difference was not statistically significant (median 58.9 months compared with 54.2 months; p=0.955).
Overall survival in the meta-analysis

The meta-analysis, STOpCaP, found that in men with metastatic prostate cancer (3 RCTs, n=2992; 1271 deaths), overall survival was statistically significantly increased in the docetaxel group compared with the ADT alone group, with an estimated absolute difference of 9% at 4 years (estimated overall survival 49% compared with 40% respectively; HR 0.77, 95% CI 0.68 to 0.87, p<0.0001; number needed to treat [NNT] 12).

In men with non-metastatic prostate cancer (3 RCTs, n=2121; 340 deaths), the difference between the groups in overall survival at 4 years did not reach statistical significance (estimated overall survival 82% with docetaxel compared with 80% with ADT alone; HR 0.87, 95% CI 0.69 to 1.09, p=0.218).

Time to clinical progression in the individual RCTs

CHAARTED and GETUG-AFU 15 found that treatment with docetaxel and ADT statistically significantly improved time to clinical progression in men with hormone-sensitive metastatic prostate cancer compared with ADT alone. This outcome was not reported for STAMPEDE.

In CHAARTED, time to clinical progression was defined as time until increasing symptoms of bone metastases and was 13.2 months longer in the docetaxel plus ADT group than the ADT alone group (median 33.0 months compared with 19.8 months respectively; HR 0.61, 95% CI 0.50 to 0.75, p<0.001).

The definition of time to clinical progression in GETUG-AFU 15 was time to death or progression of pre-existing lesions using Response Evaluation Criteria in Solid Tumours (RECIST), occurrence of new bone lesions or, in men with only bone lesions, new soft tissue lesions. Time to progression was 8.1 months longer with docetaxel plus ADT compared with ADT alone (median 23.5 months compared with 15.4 months; HR 0.75, 95% CI 0.59 to 0.94, p=0.015).

Time to biochemical progression in the individual RCTs

In men with hormone-sensitive prostate cancer, time to biochemical progression was statistically significantly improved with docetaxel plus ADT compared with ADT alone in STAMPEDE and GETUG-AFU 15. This outcome was not reported for CHAARTED.

The definition of time to biochemical progression (reported as failure-free survival) in STAMPEDE was time until death from prostate cancer, biochemical failure (according to specified criteria showing deterioration in PSA; James ND et al. 2015), or progression locally, in lymph nodes or in
distant metastases. It was 17 months longer with docetaxel plus ADT compared with ADT alone in the total population with and without metastases (median 37 months compared with 20 months, and 5-year survival 38% compared with 28% respectively; HR 0.61, 95% CI 0.53 to 0.70, p<0.0001). In the subgroup of men with metastatic prostate cancer, time to biochemical progression was also statistically significantly longer in the docetaxel plus ADT group (HR 0.61, 95% CI 0.53 to 0.71, p<0.0001), but the months to progression are not reported.

In GETUG-AFU 15, time to biochemical progression was defined as time to death, PSA progression (decrease of ≥50% plus other criteria showing deterioration) or clinical progression (as defined above). The difference between the treatments groups was 10 months (median 22.9 months in the docetaxel plus ADT group and 12.9 months in the ADT alone group; HR 0.72, 95% CI 0.57 to 0.91, p=0.005).

**Time to progression in the meta-analysis**

In the STOPCaP meta-analysis, time to progression was reported as failure free survival and defined as time to biochemical failure, clinical failure (local relapse or metastases) or death from any cause. The meta-analysis reported that, in men with metastatic prostate cancer (3 RCTs, n=2992; 2204 events) at 4 years, time to progression was statistically significantly longer in men taking docetaxel plus ADT compared with ADT alone, with an estimated absolute difference of 16% (estimated treatment failure 64% compared with 80% respectively; HR 0.64, 95% CI 0.58 to 0.70, p<0.0001; NNT 7).

Docetaxel plus ADT also statistically significantly improved time to disease progression by an estimated absolute 8% at 4 years in men without metastases (4 RCTs, 2348 men; 851 events; estimated treatment failure 22% compared with 30% with ADT alone; HR 0.70, 95% CI 0.61 to 0.81, p<0.0001, NNT 13).

**Safety and tolerability**

**Randomised controlled trials**

In the docetaxel plus ADT arm of STAMPEDE, 77% of men received the planned 6 cycles of docetaxel and, in men who received less than 5 cycles, toxicity was the main reason for stopping treatment. About 74% of men in CHAARTED received all 6 planned cycles without dose modification. In GETUG-AFU 15, 48% of men received the maximum 9 cycles of treatment: the median number of cycles was 8.

In STAMPEDE and GETUG-AFU 15 respectively, 13.1% (72/550) and 20.6% (39/189) of men taking
docetaxel plus ADT discontinued treatment due to adverse events. Results were not reported for ADT alone, and this outcome was not reported in CHAARTED. Four deaths in GETUG-AFU 15, 1 death in CHAARTED and 8 deaths (1 in the docetaxel plus ADT group, and 7 in the docetaxel and zoledronic acid plus ADT group) in STAMPEDE were considered possibly or probably related to docetaxel treatment.

Grade 3–5 adverse events (for example, events that result in death or are life threatening, result in hospital admission or extension of hospital stay or cause permanent disability or temporary incapacity: Common terminology criteria for adverse events) were reported in 38.1% of men taking docetaxel plus ADT in GETUG-AFU 15 (72/189 compared with 0/1228 with ADT alone), 29.5% of men in CHAARTED (115/390; results for ADT alone not reported) and 52.4% of men in STAMPEDE (288/550 compared with 399/1288 [32.5%] with ADT alone). Statistical analyses were not reported.

Neutropenia was reported in 49.7% (94/189) of men taking docetaxel plus ADT in GETUG-AFU 15 compared with compared with 2.7% (5/186) taking ADT alone. Grade 3–5 neutropenia was reported in 32.3% (61/189) of men taking docetaxel plus ADT and none taking ADT alone over the course of the RCT. Following the 4 deaths in the docetaxel plus ADT group, the independent data monitoring committee recommended use of granulocyte colony stimulating factor (G-CSF) following docetaxel. The number of men experiencing grade 3–5 neutropenia subsequently fell from 41% to 15% and no more deaths were recorded. In the 2 later RCTs in which G-CSF could be used throughout (although data on use was not reported), grade 3–5 neutropenia was reported in 12% of men taking the combination (47/390 in CHAARTED [results for ADT alone not reported] and 66/550 in STAMPEDE compared with 6/1288 [0.5%] with ADT alone [statistical analysis not reported]).

Summary of product characteristics

According to the summary of product characteristics for Taxotere, the originator brand of docetaxel, the adverse effects most commonly reported with docetaxel 75 mg/m² when used for prostate cancer (in combination with prednisone or prednisolone) are neutropenia (32%), anaemia (4.9%), fatigue (3.9%), infection (3.3%), nausea (2.4%), vomiting (1.2%), diarrhoea (1.2%) and peripheral sensory neuropathy (1.2%).

Evidence strengths and limitations

The 3 prospective open-label RCTs provide data for a relatively large number of men who received docetaxel for hormone-sensitive metastatic prostate cancer. STAMPEDE is directly applicable to the UK population.
**STAMPEDE** and **CHAARTED** found that docetaxel plus ADT statistically significantly improved overall survival compared with ADT alone in men with hormone-sensitive metastatic prostate cancer. However, no difference was seen between the groups in **GETUG-AFU 15**. The authors of **GETUG-AFU 15** suggest that there could be several reasons for this. For example, the RCT may have had insufficient **statistical power** to detect differences between the groups, or crossover use of docetaxel in the ADT alone group when prostate cancer became hormone-resistant may have **confounded** detection of treatment benefits.

There are differences between the RCTs that make it difficult to compare the results; for example, the numbers of men with high volume compared with low volume metastases, the proportions of men with metastatic disease at diagnosis or following treatment for localised disease, the number of cycles of docetaxel treatment, and the length of follow-up (see **table 1**). The number of men with metastases at diagnosis was high in all 3 RCTs (60–70% compared with 25% in the general population; NICE clinical knowledge summary: **prostate cancer**). A proportion of men in all the RCTs received docetaxel at development of hormone-resistant metastatic prostate cancer, which suggests the results are generalisable to clinical practice.

It is currently unclear whether or not the benefits of docetaxel are more apparent in men with metastatic compared with non-metastatic hormone-sensitive prostate cancer. In **STAMPEDE**, a pre-planned subgroup analysis in men with metastatic disease found that docetaxel plus ADT statistically significantly improved overall survival by 15 months in this population compared with ADT alone. However, similar comparisons in men with non-metastatic disease at randomisation are unreliable at the time of publication of the RCT because the number of deaths is low in the limited follow-up period. Analyses in men with recurrent (rather than newly diagnosed) prostate cancer are also underpowered. However, the evidence is likely to become clearer with longer follow-up.

The **STOpCaP** meta-analysis found similar results. In men with hormone-sensitive metastatic prostate cancer, overall survival was statistically significantly increased at 4 years with docetaxel plus ADT compared with ADT alone, but there was no significant difference between the groups in men with non-metastatic prostate cancer. However, the smaller number of deaths in men without metastases means the analysis is probably underpowered to detect a difference between the groups. Longer follow-up is needed to better assess the benefits of docetaxel in men with non-metastatic prostate cancer. The authors of **STAMPEDE** note that death from causes other than prostate cancer is more common in this population than in men with metastatic disease; therefore, any effect of docetaxel on overall survival will be diluted.

The authors of **CHAARTED** state that the benefit in terms of overall survival with docetaxel plus ADT was more apparent in the subgroup of men with high-volume metastatic disease (presence of...
visceral metastases or at least 4 bone lesions with at least 1 beyond the vertebral bodies and pelvis) compared with the overall metastatic population (difference between the treatment groups 17 months compared with 13.6 months respectively). However, the 95% confidence intervals (the range of results that is likely to include the 'true' value) for the hazard ratios for the comparisons between the treatment groups are very similar for the overall population (median 57.6 months compared with 44.0 months respectively; HR 0.61, 95% CI 0.47 to 0.80, p<0.001) and the high-volume disease population (median 49.2 months with docetaxel plus ADT compared 32.2 months with ADT alone; HR 0.60, 95% CI 0.45 to 0.81, p<0.001). Consequently, firm conclusions about whether or not overall survival in the 2 populations is similar cannot be made. At the time of the assessments, median survival had not been reached in the population with low-volume disease in either treatment group so appropriate analyses could not be undertaken.

All 3 RCTs found that time to clinical and biochemical progression was statistically significantly longer with docetaxel plus ADT compared with ADT alone. Differences between the RCTs in median times may have been due to, for example, differences in study populations, definitions of time to progression or availability of newer treatments for prostate cancer. The STOpCaP meta-analysis found that time to disease progression was statistically significantly longer in men taking docetaxel plus ADT compared with ADT alone in subgroups of men both with and without metastatic prostate cancer.

The RCTs reported various other outcomes and subgroup analyses but many are considered exploratory or possibly underpowered and should be considered with caution. However, a pre-planned appropriately powered analysis in STAMPEDE found that time to the first skeletal-related adverse event was improved with docetaxel plus ADT compared with ADT alone in the study population. There were no statistically significant differences between the groups in time to first of any treatment or life extending treatment (docetaxel, abiraterone, cabazitaxel, enzalutamide or radium-223) following disease progression, although patterns of treatment differed depending on whether docetaxel had been used before. GETUG-AFU 15 found that time to subsequent treatment was 4.6 months longer with docetaxel plus ADT compared with ADT alone but no statistical analysis was reported. CHAARTED reported that the time to development of hormone-resistant prostate cancer was statistically significantly longer with docetaxel plus ADT compared with ADT alone.

Little information is available on quality of life. GETUG-AFU 15 reported that, although quality of life was statistically significantly impaired during docetaxel treatment, global scores were generally similar between the combination and ADT alone groups at 12 months. STAMPEDE is expected to report on patient-reported outcomes in due course.
Grade 3–5 adverse events including deaths were reported following docetaxel treatment in all 3 RCTs. As in these RCTs (see table 1), participants in clinical studies have to meet inclusion criteria and typically have better performance status and prognosis, and less comorbidity than the general population. They may also be followed up more regularly. Therefore, it is possible that the adverse effect profile of docetaxel may be worse in clinical practice and, although the adverse event profile of docetaxel is well-established and the majority of participants in the RCTs tolerated the prescribed dose for the required number of cycles, caution should be used in men with comorbidity and poor performance status, and men undergoing docetaxel treatment should be carefully monitored for toxicity. The toxicity of docetaxel was particularly high in GETUG-AFU 15 before C-CSF was used to improve tolerability. The authors of STAMPEDE suggest that early use of G-CSF should be considered.

**Context and estimated impact for the NHS**

**Cost effectiveness**

No studies were identified on the cost-effectiveness of docetaxel for hormone-sensitive metastatic prostate cancer. STAMPEDE considered cost-effectiveness and this will be reported in due course.

In the 3 RCTs included in this evidence summary, docetaxel 75 mg/m² was administered every 3 weeks, usually for 6 cycles. This is the same dose that is indicated for hormone-resistant metastatic prostate cancer. Assuming the average body surface area of a man requiring docetaxel treatment is 1.91 m² (Sacco et al. 2010), the approximate dose of docetaxel is 140 mg, which costs £1023 if 1 x 2 ml vial plus 3 x 0.5 ml vials containing 40 mg/ml are used. The cost of 6 cycles of docetaxel treatment is, therefore, approximately £6138 per person (MIMS, December 2015). This is the cost of docetaxel only (excluding VAT) and does not include any procurement discounts or other costs incurred, such as dilution and administration, or standard supportive therapy. Costs may vary depending on local procurement arrangements.

**Current drug usage**

According to a report on top treatment regimens from the Systemic anti-cancer therapy (SACT) dataset, 1920 men received 8835 cycles of docetaxel for prostate cancer in NHS hospital trusts in 2014. The majority of these treatments are likely to have been for the licensed indication, hormone-resistant metastatic prostate cancer. The report also includes data on men receiving treatment in the STAMPEDE RCT and shows 130 men received 1072 cycles of docetaxel in 2014.
Relevance to NICE guidance programmes

The use of docetaxel for hormone-sensitive metastatic prostate cancer is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

NICE has produced a guideline on prostate cancer: diagnosis and management (NICE guideline CG175, 2014). See also the NICE pathway on prostate cancer and the related NICE quality standard on prostate cancer (NICE quality standard 91, 2015).

NICE guidance is available for the following licensed indications for docetaxel:

- **Docetaxel for the treatment of hormone-refractory metastatic prostate cancer** (2006) NICE technology appraisal 101

NICE guidance relating to the management of prostate cancer includes:

- **Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen** (2014) NICE technology appraisal 316
- **Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen** (2012) NICE technology appraisal 259
- **Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen** (2012) NICE technology appraisal 255 (currently being updated, anticipated publication date May 2016).

Other relevant NICE guidelines, interventional procedure guidance, technology appraisal guidance, diagnostics guidance, guidance in development, quality standards and advice are collated on the prostate cancer page of the NICE website.

A NICE clinical knowledge summary on prostate cancer (2011) provides useful information on prostate cancer and its management but is not NICE guidance and does not yet include recent NICE guidance.
References


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Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.
Expert advisers

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Declarations of interest

Simon Crabb has received honoraria from Bayer and Astellas, and research funding from AstraZeneca. He has undertaken consulting or advisory roles for Bayer, Sanofi, Astellas Pharma and Janssen Pharmaceuticals.

Peter Hoskins has been reimbursed for research studies and received grants from various companies including Millenium, Astellas Pharma, Ipsen and Amgen, Medivation and Bayer.

Liz Toy is currently involved in studies sponsored by Novartis, Amgen, AstraZeneca, Bristol Myers Squibb, Pfizer and Boehringer Ingelheim. She has been on advisory boards and clinical guideline development groups for Lilly Oncology, Roche Oncology, Pierre Fabre, Boehringer Ingelheim and AstraZeneca, undertaken educational talks as part of promotional events by Roche Oncology, Otsuko and Pierre Fabre and attended conferences funded by Boehringer Ingelheim and Roche Oncology.

Alan Lamont, David Thomson, Jonathan Waxman, Matthew Wheater and James Wylie declared no
relevant interests.

About this evidence summary

‘Evidence summaries: unlicensed or off-label medicines’ summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, but this summary is not NICE guidance.

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