



**Clinical Commissioning Policy  
Statement: Docetaxel in  
combination with androgen  
deprivation therapy for the  
treatment of hormone naïve  
metastatic prostate cancer**

NHS England Reference: [B15/PS/a]

**NHS England INFORMATION READER BOX****Directorate**

Medical	<b>Commissioning Operations</b>	Patients and Information
Nursing	Trans. & Corp. Ops.	Commissioning Strategy
Finance		

**Publications Gateway Reference:****04680**

<b>Document Purpose</b>	Policy
<b>Document Name</b>	Docetaxel in combination with androgen deprivation therapy for the treatment of hormone naïve metastatic prostate cancer
<b>Author</b>	Specialised Commissioning Team, NHS England
<b>Publication Date</b>	20 January 2016
<b>Target Audience</b>	Local Team Assistant Directors of Specialised Commissioning; Regional Team IFR Leads; Finance Leads; Local Team Pharmacists; Chairs of Clinical Reference Groups; Members of Clinical Reference Groups and registered stakeholders; Acute Trust Chief Executives; Acute Trust Medical Directors; Acute Trust Chief Pharmacists
<b>Additional Circulation List</b>	Regional Medical Directors; Regional Directors of Specialised Commissioning; Regional Clinical Directors of Specialised Commissioning; Regional Directors of Nursing
<b>Description</b>	NHS England will routinely commission this specialised treatment in accordance with the criteria described in this policy.
<b>Cross Reference</b>	
<b>Superseded Docs</b> (if applicable)	
<b>Action Required</b>	
<b>Timing / Deadlines</b> (if applicable)	
<b>Contact Details for further information</b>	england.specialisedcommissioning@nhs.net

**Document Status**

This is a controlled document. Whilst this document may be printed, the electronic version posted on the intranet is the controlled copy. Any printed copies of this document are not controlled. As a controlled document, this document should not be saved onto local or network drives but should always be accessed from the intranet. **NB:** The National Health Service Commissioning Board was established on 1 October 2012 as an executive non-departmental public body. Since 1 April 2013, the National Health Service Commissioning Board has used the name NHS England for operational purposes.

## Contents

1 Plain Language Summary.....	4
2 Background.....	4
3 Commissioning Position.....	5
3.1 Indications .....	5
3.2 Dose .....	6
3.3 Contra-indications .....	6
3.4 Exclusions .....	7
3.5 3.4 Starting and stopping criteria .....	7
4 Effective from .....	8
5 Evidence Summary .....	8
5.1. Overview of Clinical Evidence.....	8
5.2. Clinical Effectiveness.....	9
5.3. Safety .....	10
5.4. Patient factors .....	10
6 Cost.....	11
7 Equality statement .....	11
8 Mechanism for funding .....	11
9 Responsible CRG.....	11
10 Date approved .....	12
11 Policy review date .....	12
12 Links to other Policies .....	12
13 References .....	12

## 1 Plain Language Summary

Prostate cancer is the most common cancer in men in the UK and about 1 in 8 men will get prostate cancer at some point in their lives. Older men, men with a family history of prostate cancer and Black men are more at risk of developing the disease.

More than 38,000 men are diagnosed with prostate cancer and more than 9,000 men die from the disease every year in England (ONS 2015). At the point of diagnosis approximately 4,560 (12%) of cases are metastatic.

Prostate cancer can spread to any part of the body, but it most commonly spreads to the bones and lymph nodes. Advanced (metastatic) prostate cancer can cause symptoms such as bone pain, loss of well-being and problems urinating. It is not possible to cure advanced prostate cancer but treatments, such as initial hormone therapy (i.e., Androgen Deprivation Therapy [ADT]), can keep it under control, sometimes for several years.

Docetaxel chemotherapy is a routine treatment for men with advanced prostate cancer, however under current guidelines (NICE TA101) it is prescribed only after men who have become resistant to ADT. This policy statement has been developed to enable men with advanced prostate cancer to receive docetaxel at the same time as starting ADT, i.e., when they are 'hormone naïve'.

NHS England has reviewed the evidence and concluded that it is sufficient to enable docetaxel to be routinely funded for the treatment of newly-diagnosed hormone naïve metastatic prostate cancer, where treatment with docetaxel is started within 12 weeks of commencing treatment with ADT.

## 2 Background

This policy statement has been developed because recently available results from clinical trials, including a major NHS-led trial, have shown that when men who are diagnosed with metastatic prostate cancer are given docetaxel at the same time as ADT they have an improved overall survival benefit of up to 15 months longer, when compared to current practice.

Using docetaxel to treat hormone naïve prostate cancer is an off-label use of the drug. The term 'off-label' is used where clinicians prescribe approved medications to treat conditions beyond the medicine's licensed purpose. The evidence for this new use of docetaxel is

based on analysis of overall survival (OS) data obtained from a clinical trial. OS is a measure used in clinical trials to demonstrate the additional months, or years, of life gained from taking a treatment.

### **3 Commissioning Position**

NHS England will commission docetaxel for the treatment of hormone naïve metastatic prostate cancer in accordance with the criteria outlined in this document.

In the context of this policy, the term ‘hormone-naïve’ refers to patients that are about to start (or who have started within the last 12 weeks) treatment with ADT for the treatment of metastatic prostate cancer. This is similar to the term ‘hormone-sensitive’, which is essentially a broader population that refers to all men with metastatic prostate cancer that are receiving hormone treatment, which can work for many years. The published evidence base for docetaxel treatment for metastatic prostate cancer draws upon a number of randomised control trials (RCTs) which indicated an overall survival benefit for men that are yet to start (or who have started within 12 weeks) treatment with ADT.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy statement outlines the arrangements for funding of this treatment for the population in England.

Clinical criteria have been developed to ensure effective use of docetaxel.

#### **3.1 Indications**

Docetaxel is not licensed to treat this indication and is therefore ‘off label’. In order to use medicines that are unlicensed, or used for an unlicensed indication, each provider organisation must assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust’s Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

In order to support shared decision-making and informed consent, the risks and benefits regarding the off label use of docetaxel for this treatment should be clearly stated and discussed.

Docetaxel should be used to treat hormone naïve metastatic prostate cancer, as follows, in:

- Men either commencing, or who have commenced within 12 weeks, long-term ADT for metastatic disease for the first time; and
- Men of sufficient performance status to be treated with 6 cycles of docetaxel chemotherapy.

### **3.2 Dose**

In accordance with the published evidence base, 75 mg/ m<sup>2</sup> of docetaxel should be administered every 3 weeks for 6 cycles, in conjunction with prednisolone 5mg twice daily for 3 weeks.

Where patients develop febrile neutropenia as a result of treatment with docetaxel, treating clinicians should manage the condition with dose reduction protocols and/or (depending on the treating Trust's policy on the use of granulocyte colony stimulating factors [GCSF]). The Summary of Product Characteristics for docetaxel outlines the following general dose requirements and adjustments.

Treatment should be discontinued where reactions persist at the 60 mg/ mg/m<sup>2</sup> dose.

### **3.3 Contra-indications**

There are few absolute contra-indications for docetaxel therapy. However, an absolute contra-indication is severe prior hypersensitivity reaction to taxanes.

Other contra-indications would include, poor overall performance status (WHO performance status 3-4, caution for those with performance status 2), pre-existing significant peripheral neuropathy, poor bone marrow function due to extensive disease or other prior haematological problems, significant co-morbidity (e.g. cardio-vascular or respiratory disease) such that prostate cancer is not likely to be the life limiting illness for the patient.

### 3.4 Exclusions

See contra-indications above.

### 3.5 Starting and stopping criteria

#### Starting criteria:

Patients will be eligible for treatment under this policy who:

- have newly diagnosed metastatic, prostate cancer;
- are either commencing, or who have commenced within 12 weeks, long-term hormone therapy (Androgen Deprivation Therapy) for metastatic disease for the first time; and
- have sufficient performance status to be treated with 6 cycles of docetaxel chemotherapy.

#### Stopping criteria:

Unlike most cancer chemotherapies, docetaxel in the hormone naïve context is given while men are responding to their ADT. Most patients will thus stop docetaxel for reasons either for toxicity or from patient preference. Formal stopping rules are as follows:

- Disease progression on treatment (this is likely to be rare);
- Toxicity precluding safe administration of further therapy (e.g. severe sepsis, grade 3 neuropathy);
- Patient request; and
- At the end of 6 cycles of treatment.

Docetaxel is a widely used drug in this patient population, hence clinicians are familiar with the safe use and stopping rules for the agent.

Following treatment with docetaxel, men will continue with ADT until the disease becomes resistant to this treatment. This policy statement does not impact on the current standard of care where prostate cancer has become resistant to ADT. The current standard of care includes abiraterone, enzalutamide and docetaxel (in accordance with NICE TA101).

## 4 Effective from

January 2016.

## 5 Evidence Summary

To support the development of this policy statement, NHS England commissioned the National Institute for Health and Care Excellence (NICE) to review the evidence for docetaxel in patients with hormone-sensitive metastatic prostate cancer (NICE, 2016).

### 5.1. Overview of Clinical Evidence

The NICE 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 (Gravis et al.2013), n=385 and CHAARTED (Sweeney et al. 2015), n=790 enrolled men with metastatic prostate cancer. The third, STAMPEDE (James et al.2015), 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 the NICE evidence summary. The study designs and methods, and the baseline characteristics of the participants in the 3 RCTs are outlined in greater detail in the NICE summary (NICE, 2016).

A systematic review and meta-analysis (STOpCaP) (Vale et al. 2015) 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 the NICE 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, CHAARTED, STAMPEDE, 1 not published and 1 ongoing), 3 of which (GETUG-AFU 15, CHAARTED and STAMPEDE) reported the outcomes of interest



(n=2992). The RCTs used docetaxel 75 mg/m<sup>2</sup> every 3 weeks for 6 or 9 cycles for a median of 29 to 82.9 months. The median age of the participants was 63–65 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, 5 not published and 2 ongoing), 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/m<sup>2</sup> every 3 weeks for 6 cycles and the other used 70 mg/m<sup>2</sup> per cycle plus estramustine. The median age of the men was 62–66 years. Median follow-up was 39 to 82.9 months. The included RCTs were assessed as being at low risk of bias.

## 5.2. Clinical Effectiveness

The NICE review concludes that the randomised controlled trial (RCT) data suggests 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 up to 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. Key findings include:

- In 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 and without 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)

- 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).

### 5.3. Safety

The toxicity of docetaxel is well-established. The summary of product characteristics (SPC) for Taxotere®, the originator brand of docetaxel, outlines that the adverse effects most commonly reported with docetaxel 75 mg/m<sup>2</sup> 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%).

All three studies demonstrated that most participants tolerated the planned number of docetaxel treatment cycles, though in some cases this was achieved with dose reduction and GCSF to manage toxicity. The review of the evidence (NICE, 2016) indicates that the study findings align to the adverse effects stated within the SPC.

All three studies reported patient deaths that were considered possibly or probably related to docetaxel treatment, as follows:

- GETUG-AFU 15: four deaths;
- CHARTED: one death; and
- STAMPEDE: eight deaths (1 with docetaxel plus ADT and 7 with docetaxel, zoledronic acid and ADT).

### 5.4. Patient factors

The following patient factors were identified:

- 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 CHARTED.
- In the 3 RCTs, half to three quarters of men tolerated the study dosage of docetaxel for the planned treatment duration (75 mg/m<sup>2</sup> 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.

- 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.

## **6 Cost**

The cost of implementing the commissioning policy statement is driven by both the cost of docetaxel and the supportive drugs associated with this treatment, together with the cost of chemotherapy delivery. In addition, a small number of patients may require additional district nursing support. These costs are partially offset by some savings associated with reducing skeletal events, such as bone fracture.

## **7 Equality statement**

NHS England has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012. NHS England is committed to fulfilling this duty as to equality of access and to avoiding unlawful discrimination on the grounds of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, gender or sexual orientation. In carrying out its functions, NHS England will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which NHS England is responsible, including policy development, review and implementation.

## **8 Mechanism for funding**

NHS England standard contract arrangements will apply. All use of docetaxel must be recorded on the SACT database.

## **9 Responsible CRG**

Chemotherapy CRG.

## 10 Date approved

13<sup>th</sup> January 2016

## 11 Policy review date

The policy statement will be revised during 2016/17 with the publication of a clinical commissioning policy.

## 12 Links to other Policies

This policy statement follows the principles set out in the ethical framework that govern the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

## 13 References

Gravis G, Fizazi K, Joly F et al. (2013) Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. *Lancet Oncology* 14: 149–58

James ND, Spears MR, Clarke NW et al. (2015) Survival with newly diagnosed metastatic prostate cancer in the “docetaxel era”: data from 917 patients in the control arm of the STAMPEDE trial. *European Urology* 67: 1028–38

James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, Ritchie AWS, Parker CC, Russell JM, Attard G, de Bono J, Cross W, Jones RJ, Thalmann G, Amos C, Matheson D, Millman R, Alzouebi M, Beesley S, Birtle AJ, Brock S, Cathomas R, Chakraborti P, Chowdhury S, Cook A, Elliott T, Gale J, Gibbs S, Graham JD, Hetherington J, Hughes R, Laing R, McKinna F, McLaren DB, O’Sullivan JM, Parikh O, Peedell C, Protheroe A, Robinson AJ, Srihari N, Srinivasan R, Staff urth J, Sundar S, Tolan S, Tsang D, Wagstaff J, Parmar MKB. 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. *The Lancet* S0140-6736(15) 01037-5

National Institute for Health and Care Excellence (2015). Evidence Summary for NHS England. Hormone-sensitive metastatic prostate cancer: docetaxel.

Office for National Statistics (2015) Cancer registration statistics, England, 2013 [online; accessed 3 December 2015]

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

Vale CL, Burdett S, Rydzewska LHM, Albiges L, Clarke NW, Fisher D, Fizazi K, Gravis G, James ND, Mason MD, Parmar MKB, Sweeney CJ, Sydes MR, Tombal B, Tierney JF, on behalf of the STOpCaP Steering Group (2015). Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. *Lancet Oncology* S1470-2045 (15) 00489-1