AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Evidence Status Report: abiraterone acetate for the treatment of non-metastatic and locally advanced high-risk, hormone-sensitive prostate cancer **(OW20)**

Report prepared by the All Wales Therapeutics and Toxicology Centre
September 2022

Key findings

Licence status
Abiraterone is not licensed for treating non-metastatic and locally advanced, high-risk, hormone-sensitive prostate cancer; its use for this indication is off-label.

Clinical evidence
The clinical evidence for the use of abiraterone in this setting comes from three arms of the STAMPEDE, a phase 3, multi-platform, open-label, randomised controlled trial (RCT). These are: 2 stages comparing abiraterone plus prednisolone with androgen-deprivation therapy (ADT), with or without enzalutamide; and from one stage comparing abiraterone with ADT alone.

Compared to ADT alone, abiraterone plus prednisolone with ADT showed clinical benefit in terms of failure-free survival and overall survival in de novo high-risk, non-metastatic prostate cancer. In a sub-group analysis of the STAMPEDE study, abiraterone showed similar efficacy to docetaxel.

Safety
No new safety signals have been observed for abiraterone in this indication. A network meta-analysis showed the incidence of severe adverse events was equivalent between the docetaxel and abiraterone treatment. Abiraterone has a different adverse event profile to docetaxel, with fewer immunosuppressive effects.

Patient factors
Abiraterone is taken orally as a daily dose continued until disease progression. Due to the risk of hepatotoxicity, serum transaminases should be monitored every 2 weeks for the first 3 months of starting treatment with abiraterone and monthly after that.

Cost effectiveness
A cost-utility analysis, from an NHS perspective, of adding abiraterone plus prednisolone to ADT, was compared with ADT alone. It showed that although abiraterone improved survival in non-metastatic prostate cancer, it was not cost-effective using the current BNF price for the reference product Zytiga®. No cost-effectiveness evidence was found that compared adding abiraterone or docetaxel to ADT in non-metastatic prostate cancer.

Budget impact
Using the NHS Wales contract price for generic abiraterone, the addition of

abiraterone is estimated to be [Commercial in confidence text removed] in year 1 and [Commercial in confidence text removed] in years 2 and 3, respectively. A number of scenario analyses have been undertaken and are presented in the appendices.

Impact on health and social care services
Abiraterone is expected to increase resource use due to additional monitoring requirements (see patient factors). Docetaxel requires more intensive resource use during the treatment phase in terms of consultant and chair time for administration of chemotherapy. Thereafter monitoring requirements are markedly less, with 6 monthly checks. For ADT alone monitoring is minimal with 6 monthly check ups.

Innovation and/or advantages
Abiraterone has a different adverse effect profile to docetaxel, with fewer immunosuppressive effects. It is an oral treatment that may be taken at home, unlike docetaxel, which is given intravenously.

Background

Clinicians in Wales consider there is an unmet need and have identified a cohort of patients who could benefit from this treatment. Abiraterone was therefore considered suitable for assessment though the One Wales medicines process.

The All Wales Therapeutics and Toxicology Centre (AWTTC) sought opinions from clinical experts in Wales, who said that treatment with an androgen receptor targeted agent (ARTA) is the preferred treatment choice for patients with newly diagnosed high risk non-metastatic prostate cancer. Clinical experts expressed a preference for abiraterone as, in their experience, it is better tolerated than the current treatment option (chemotherapy with off-label docetaxel). Abiraterone is also suitable for those patients who may be older or frail and would not be able to tolerate treatment with docetaxel.
The marketing authorisation holder of abiraterone is not planning to apply for a licence to use abiraterone to treat non-metastatic, high-risk, hormone-sensitive prostate cancer.

Target group

The indication under consideration is the treatment of de novo non-metastatic and locally advanced, high-risk, hormone-sensitive prostate cancer with at least two of: T3 or T4 stage, Gleason sum score 8–10, prostate specific antigens (PSA) > 40 micrograms/litre.

Marketing authorisation date: Not applicable, off-label

Abiraterone is not licensed for the treatment of non-metastatic and locally advanced, high-risk, hormone-sensitive prostate cancer.

Abiraterone is licensed for use in combination with prednisone or prednisolone to treat:

- newly diagnosed high-risk metastatic hormone-sensitive prostate cancer in combination with androgen deprivation therapy;

- metastatic castration-resistant prostate cancer in asymptomatic or mildly symptomatic patients when ADT has not worked and chemotherapy is not yet indicated; and
- metastatic castration-resistance prostate cancer that has progressed on or after a docetaxel-based chemotherapy regimen[1].

Dosing information

The recommended dose is 1,000 mg (two 500 mg tablets) taken as a single daily dose, in combination with 5 mg prednisolone daily[1].

Clinical background

Prostate cancer is the most common cancer in men in the UK, with around 52,300 cases diagnosed each year[2]. Prostate cancer is the second most common cause of cancer death in males in the UK, with around 12,000 deaths each year[2]. The type and grade of the cancer affects survival, as does the size of the cancer when it was diagnosed and whether it has spread[2].

The most common type of prostate cancer is acinar adenocarcinoma of the prostate, which develops in the cells that line the prostate gland. In the STAMPEDE clinical study high-risk prostate cancer is defined as node positive, or if node negative, having at least two of the following:

- high Gleason score of 8 to 10 (cells in the prostate gland look abnormal; the cancer is likely to grow quickly);
- T3 or T4 stage (the cancer has broken through the covering of the prostate gland [T3], or has spread into body organs nearby [T4]);
- levels of prostate-specific antigens (PSA) in the blood ≥ 40 micrograms/litre[3].

Incidence/prevalence

The 2021 prostate cancer national audit showed 2,561 cases of newly diagnosed prostate cancer in Wales during 1 April 2019 to 31 March 2020[4]. Of these, 768 men (32%) had high-risk or locally advanced disease[4].

Current treatment options and relevant guidance

The National Institute for Health and Care Excellence (NICE) guideline NG131, on the diagnosis and management of prostate cancer, recommends offering treatment of high-risk, non-metastatic, hormone-sensitive prostate cancer with a combination of radiotherapy with at least 6 months of androgen deprivation therapy (ADT), and considering continuing the ADT for up to 3 years[5]. The guideline defines ‘high risk’ as shown by:

- Gleason score of 8 to 10; **or**
- T3 or T4 staging; **or**
- PSA levels greater than 40 micrograms/litre.

NICE guideline NG131 also recommends discussing the option of using intravenous docetaxel off-label to treat newly diagnosed high-risk non-metastatic prostate cancer in patients starting long-term ADT who have no significant co-morbidities[5].

The European Society of Clinical Oncology (ESMO) clinical practice guidelines for the diagnosis, treatment and follow-up of prostate cancer recommend long-term ADT and radiotherapy with or without neoadjuvant docetaxel for treating high-risk, disease[6]. For locally advanced disease, the guidelines recommend neoadjuvant ADT

and radiotherapy, and adjuvant ADT, with or without neoadjuvant docetaxel. The ESMO guidelines define 'high risk' as:

- Gleason score of 8 to 10; **or**
- ≥T2c staging (the cancer has invaded both sides of the prostate [T2c]); **or**
- PSA levels greater than 20 micrograms/litre[6].

The National Cancer Medicines Advisory Group (NCMAG) for Scotland do not support the use of abiraterone, in combination with prednisolone and ADT for the treatment of high-risk, hormone sensitive, non-metastatic prostate cancer[7]. The NCMAG council noted that phase three study results demonstrated that abiraterone improves metastases-free survival when compared with ADT alone. However, cost effectiveness estimates did not show sufficient health benefits in relation to treatment costs to gain support. The group will re-assess the cost effectiveness once generic alternatives are available[7].

NICE recommended the use of abiraterone, in combination with prednisolone, to treat metastatic, hormone-relapsed prostate cancer in people who have no or mild symptoms after ADT has failed, and before chemotherapy is indicated[8]. NICE recommended abiraterone plus prednisolone to treat castration-resistant metastatic prostate cancer only for people whose disease has progressed on or after one docetaxel-containing chemotherapy regimen[9].

NICE did not recommend abiraterone, in combination with prednisolone and ADT, to treat newly-diagnosed high-risk hormone-sensitive metastatic prostate cancer[10]. The NICE committee noted that clinical study results showed that abiraterone plus prednisolone plus ADT increased the time until the disease progresses and how long people live compared with ADT alone; compared with docetaxel plus ADT, abiraterone plus ADT increases the time to disease progression, but not how long people live. NICE recognised that docetaxel plus ADT is unsuitable for some patients, but there was no clinical evidence for abiraterone plus ADT compared with ADT alone for the sub-group of patients with newly-diagnosed high-risk hormone-sensitive metastatic prostate cancer where docetaxel is unsuitable. Cost-effectiveness estimates of abiraterone plus prednisolone compared with ADT alone or docetaxel plus ADT were higher than what NICE considered cost effective. There were no appropriate cost-effectiveness estimates for when docetaxel cannot be used or is unsuitable[10].

Following assessment under the orphan medicine process, the Scottish Medicines Consortium (SMC) recommended the use of abiraterone, in combination with prednisolone and ADT, to treat newly diagnosed high-risk hormone-sensitive metastatic prostate cancer[11].

Summary of evidence on clinical effectiveness

AWTTC conducted a literature search and identified three reports of results from different stages of the multi-arm, multi-stage open-label, randomised controlled phase three study called "systemic therapy in advancing or metastatic prostate cancer: evaluation of drug efficacy" (STAMPEDE). An additional mixed-model assessment of patient-reported quality-of-life (QoL) data from patients enrolled in the STAMPEDE study was also identified. The three reports, three network meta-analyses, and QoL assessment based on STAMPEDE study data, are discussed below.

Efficacy

The **STAMPEDE** study was an open-label, randomised controlled trial (RCT) conducted to see if adding further treatments to ADT would improve overall survival of men with advancing or metastatic prostate cancer who were receiving first-line treatment[3]. The treatments studied included abiraterone and docetaxel. Patients enrolled in the STAMPEDE study had prostate cancer that was:

- newly diagnosed and metastatic, node-positive; **or**
- high-risk locally advanced (with at least 2 of the following: tumour stage T3 or T4, a Gleason score of 8 to 10, and a PSA level of ≥ 40 ng/ml); **or**
- disease that was previous treated but now relapsing with high-risk features (in men no longer receiving therapy, a PSA level > 4 ng/ml with a doubling time of < 6 months, a PSA level > 20 ng/ml, nodal or metastatic relapse, or < 12 months of total ADT with an interval of > 12 months without treatment)[3].

Attard et al. (2022) conducted a meta-analysis of results from two stages of the open-label phase three STAMPEDE protocol to assess the efficacy of adding abiraterone plus prednisolone alone, or with enzalutamide, to ADT in men with non-metastatic prostate cancer who were treated with ADT for three years, combined with radiotherapy[12].

In the first stage patients were randomly assigned (1:1) to receive either ADT alone (n = 455), which could include surgery and luteinising hormone-releasing hormone agonists or antagonists, or in combination with 1,000 mg/day oral abiraterone and 5 mg/day oral prednisolone (n = 459)[12]. The second stage allocated patients to ADT alone (n = 533) or ADT in combination with abiraterone plus enzalutamide (n = 527).

The primary outcome was metastasis-free survival (MFS), defined as the time from randomisation to death from any cause or to distant metastases confirmed by imaging, assessed by unblinded investigators, in the intention-to-treat population[12]. The median follow-up was 72 months (60–84). MFS was significantly longer in the abiraterone with or without enzalutamide combination therapy group (median not reached) than in the ADT-alone group (median not reached, hazard ratio [HR] 0.53, 95% confidence interval [CI] 0.44 to 0.64; p < 0.0001). Overall survival, a secondary outcome; was significantly longer in the abiraterone with or without enzalutamide combination therapy groups (median not reached) compared with the ADT-alone group (median not reached; HR 0.60, 95% CI 0.48 to 0.73; p < 0.0001). Six-year survival improved from 77% in the ADT-alone group to 86% in the abiraterone groups.

A pre-planned subgroup analysis showed a consistent overall effect for abiraterone: hazard ratio (HR) 0.54, 95% CI 0.43 to 0.68; p < 0.0001). Analysis of the results from both studies showed no benefit of adding enzalutamide to abiraterone (interaction HR 1.02, 95%CI 0.7 to 1.5; p = 0.91)[12].

James et al. (2017) investigated the effect of giving abiraterone plus prednisone compared with ADT alone[3]. A total of 1,917 patients were randomised to receive either abiraterone (1,000 mg/day) plus prednisone (5 mg/day) plus ADT (n=960), or ADT-alone (n = 957)[3]. Just over half (52%) of the patients had metastatic disease; 20% had node-positive or node-indeterminate non-metastatic disease and 28% had node-negative non-metastatic disease. The median follow-up time was 40 months[3].

There were 184 deaths in the combination group and 262 in the ADT-alone group. The results showed a survival advantage in the abiraterone group; three-year survival was 83% in the abiraterone group compared with 76% in the group receiving ADT alone (hazard ratio [HR] for death, 0.63; 95% CI, 0.52 to 0.76; p < 0.001). There were 248 treatment-failure events in the combination group compared with 535 in the ADT-alone group[3].

The three-year failure-free survival was 75% in the abiraterone group and 45% in the ADT-alone group (HR, 0.29; 95% CI, 0.25 to 0.34; p < 0.001)[3]. Due to evidence of nonproportional hazards, the restricted mean failure-free time was presented; 43.9 months in the abiraterone group and 30.0 months in the ADT-alone group in the first 54 months after randomisation, a difference of 13.9 months (95% CI: 12.3 to 15.4). This effect was noted across all patient sub-groups[3].

The use of ADT plus abiraterone and prednisolone as compared with ADT alone was associated with a 71% relative improvement in the time to treatment failure, which translated into a 37% difference in overall survival[3]. These findings were consistent in patients with metastatic disease and those with non-metastatic disease. In the non-metastatic sub-group, 34 of 460 patients died in the abiraterone group and 44 of 455 patients died in the ADT-alone group (HR 0.75; 95% CI: 0.48 to 1.18). In the metastatic subgroup, 150 of 500 patients died in the abiraterone group and 218 of 502 patients died in the ADT-alone group (HR 0.61; 95% CI: 0.49 to 0.75)[3].

For failure-free survival, the numbers of treatment-failure events in the non-metastatic subgroup were 38 of 460 in the abiraterone group and 142 of 445 in the ADT-alone group (HR 0.21; 95% CI: 0.15 to 0.31)[3]. In the metastatic subgroup treatment failure events were 210 of 500 and 393 of 502 (HR 0.31; 95% CI: 0.26 to 0.37). No statistically significant differences were demonstrated between metastatic and non-metastatic subgroups in OS (p = 0.37) or failure free survival (p = 0.08)[3].

An overlap of 17 months in recruitment to the abiraterone and docetaxel stages of the STAMPEDE trial gave an opportunity to compare these two treatments[13]. Patients (n = 566) randomised to receive abiraterone plus prednisolone (n = 377) or docetaxel plus prednisolone (n = 189) during this overlap period were included in the analysis. The median follow-up was calculated as 48 months. There was no significant difference in overall survival; 105 of 377 patients (28%) died in the abiraterone group and 44 of 189 patients (23%) died in the docetaxel group (HR 1.16; 95% CI: 0.82 to 1.65; p = 0.40). There were 150 patients in the abiraterone group and 74 patients in the docetaxel group who had non-metastatic disease. For overall survival there was no evidence of interaction of treatment effect by baseline metastatic (HR 1.13, 95% CI 0.77 to 1.66) and non-metastatic (HR 1.51, 95% CI 0.58 to 3.93) patient sub-populations (p = 0.69) [13].

Network meta-analyses

Rajwa et al. (2022) conducted a network meta-analysis (NMA) to assess the outcomes associated with adding combination systemic treatment to primary definitive local therapy in patients with high-risk and/or unfavourable non-metastatic prostate cancer[14]. A total of 15 studies were identified. The NMA comparing docetaxel-based and androgen receptor signalling inhibitor (ARSI) treatment with ADT alone included 890 patients treated with docetaxel and ADT, 459 patients treated with abiraterone and ADT, 527 treated with abiraterone, enzalutamide and ADT, and 2,109 treated with ADT alone[14].

Compared with ADT alone, abiraterone and ADT (with or without enzalutamide) were significantly associated with better overall survival, cancer-specific survival, metastasis-free survival, and failure-free survival; docetaxel plus ADT met the statistical significance threshold only for failure-free survival[14]. Compared with docetaxel plus ADT, abiraterone plus ADT was associated with significantly better overall survival (HR 0.69, 95% CI 0.50 to 0.95), metastasis-free survival (HR 0.63, 95% CI 0.45 to 0.88) and failure-free survival (HR 0.53, 95% CI 0.41 to 0.70). According to analysis of the ranking for overall survival, the preferred treatment probability was 91% for abiraterone plus enzalutamide plus ADT, 75% for abiraterone plus ADT, 29% for docetaxel plus ADT, and 5% for ADT alone. For metastatic-free survival, the surface under the cumulative ranking (SUCRA) results showed that the preferred treatment probability was 85% for abiraterone plus enzalutamide plus ADT, 82% for abiraterone plus ADT, 32% for docetaxel plus ADT, and 1.5% for ADT alone[14].

Sun et al. (2018) conducted a network meta-analysis that included data from the STAMPEDE study. It concluded that combination treatment with ADT and docetaxel or abiraterone could extend failure-free survival in men with non-metastatic castration-naïve prostate cancer[15]. However, the data were immature for overall survival[15]. **Wallis et al.** (2018) conducted a network meta-analysis that looked at the comparison data for docetaxel and abiraterone from the STAMPEDE study. The hazard ratio for overall survival in the non-metastatic prostate cancer group was 0.79 (95% CI: 0.42–1.47). Indirect comparison of abiraterone with ADT to docetaxel with ADT demonstrated no significant difference in overall survival (HR 0.84, 95% CI 0.67 to 1.06)[16].

Quality of life

Rush et al (2021) conducted a mixed-model assessment of patient-reported QoL in patients enrolled in the STAMPEDE study and who had completed at least one EORTC QLQ-C30 with the prostate cancer-specific module (PR25)[17]. Patients with high risk locally advanced (non-metastatic) or metastatic hormone sensitive prostate cancer were randomly allocated to receive either docetaxel with ADT (n = 173), abiraterone plus prednisolone with ADT (n = 342) or ADT alone (343). Questionnaires were completed at baseline, at follow-up visits up to five years and annually thereafter. Primary endpoint results were reported as the difference in global QoL scores over two years between the docetaxel group and the abiraterone group[17].

Over the two years the mean-modelled global-QoL score was 3.9 points (95% CI 0.5 to 7.2, p = 0.22) higher in the abiraterone group[17]. This narrowly missed the predefined threshold of a > 4.0-point difference for clinical meaningful significance. Over the first year global-QoL was higher for the abiraterone group (5.7 points, 95% CI 3.0 to 8.5, p < 0.001)[17].

There was a similar proportion of patients with non-metastatic disease in the docetaxel group (n = 71, 41%) and the abiraterone group (n = 137, 40%), results showed no clear evidence of a significant difference in scores (+3.0, 95% CI -2.4 to 8.3, p = 0.275)[17]. For the metastatic subpopulations there was evidence of higher global QoL scores in the abiraterone group (+4.5 points, 95% CI 0.3 to 8.6, p = 0.36). An interaction test found no evidence that metastatic status had a differential effect on the difference between QoL scores for the two treatment groups (interaction p = 0.701)[17].

There was no difference between global-QoL scores over two years in the docetaxel group compared with the ADT alone group (-1.0 points, 95% CI -4.4 to 2.3, p = 0.553), scores for the abiraterone group were higher than the ADT alone group although they did not meet the clinically meaningful difference threshold (2.9 points, 95% CI 0.1 to 5.6, p = 0.40)[17].

Safety

In the two STAMPEDE stages reported by Attard et al. (2022), grade three or worse adverse events were reported during the first 24 months by 37% of patients in the abiraterone plus ADT group, and by 29% of patients in the corresponding ADT-alone group[12]. Three grade five events were reported in the abiraterone plus ADT group: these were rectal adenocarcinoma, pulmonary haemorrhage and a respiratory disorder. The most common grade three events or worse reported in the abiraterone with or without enzalutamide groups were hypertension (41% versus 5% in the ADT-alone group) and increased aminotransferases 34% versus 14% in the ADT-alone group)[12].

In the STAMPEDE stage reported by James et al. (2017), grade three to five adverse events occurred in 47% of patients in the combination group, and in 33% of patients in the ADT-alone group, including three grade five events (deaths)[3]. In the abiraterone group, there were nine grade five events (treatment-related deaths): two events of pneumonia (one including sepsis), two events of stroke; and one event each of dyspnoea, lower respiratory tract infection, liver failure, pulmonary haemorrhage and chest infection. In the ADT-alone group, there were three treatment-related deaths: two grade five events of myocardial infarction and one event of bronchopneumonia. The main grade three to five adverse events in the abiraterone group that occurred more often than in the ADT-alone group were: hypertension (5%), mild increases in aminotransferase levels (7%) and respiratory disorders (5%)[3].

In the STAMPEDE study arms that compared abiraterone and docetaxel, among all patients who started their allocated treatment (the safety population) the proportions of patients who reported an adverse event were similar in both groups. The proportions reporting one or more grade three, four or five adverse events were 36%, 13% and 1% in the docetaxel plus standard care group, compared with 40%, 7% and 1% in the abiraterone and prednisone plus standard care group[13]. The prevalence of grade three or four toxicity in patients was 11% in both arms after one and two years[13].

Sun et al. (2018) conducted a meta-analysis of data from the STAMPEDE stages comparing abiraterone plus ADT with docetaxel plus ADT[15]. The results showed that combination therapy increased the number of severe adverse events (grade three and above) by nearly two-fold compared with ADT alone (HR: 1.96; 95% CI 1.74 to 2.20; p < 0.00001). However, the incidence of severe adverse events was equivalent between the docetaxel and abiraterone combination treatment groups (HR: 1.16, 95% CI 0.92 to 1.48; p > 0.05)[15].

The Summary of Product Characteristics (SmPC) for abiraterone lists very common (occurring in ≥ 1 in 10 people) adverse reactions as: urinary tract infections; hypokalaemia; hypertension; diarrhoea; increased alanine aminotransferase and/or increased aspartate aminotransferase; and peripheral oedema[1]. The SmPC recommends that serum transaminases should be monitored every two weeks for the first three months of starting treatment with abiraterone and monthly after that[1].

The SmPC warns that abiraterone may cause hypertension, hypokalaemia and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition[1]. Blood pressure, serum potassium and fluid retention should be monitored monthly[1].

Discussion

Evidence for the off-label use of abiraterone to treat non-metastatic and locally advanced high-risk, hormone-sensitive prostate cancer comes from the comparison of abiraterone and docetaxel, and abiraterone and ADT, in the open-label STAMPEDE studies[3,12]. STAMPEDE predominantly recruited from the UK population, the largest recruiter was a cancer centre in Wales[18]. Concomitant treatments followed local guidelines[3,12]. All node negative patients included in the study had received radiotherapy, which is in line with NICE guidelines[5,12]. The arms of the STAMPEDE study may not capture all treatments available to patients at this time, however the results of STAMPEDE are considered to be generally relevant for patients in Wales.
The comparison with docetaxel was opportunistic; the study was not powered to detect differences between the two combination treatments. In comparison to ADT alone, abiraterone showed clinical benefit in terms of progression-free survival and overall survival[3].

The STAMPEDE platform was open-label, so there may be risk of performance bias and assessment bias and this could have affected patient-reported outcomes.

A clinically meaningful difference in QoL scores favouring abiraterone over docetaxel was reported in the first year of treatment for all high-risk hormone sensitive patients. Although the difference had narrowed to just below the significance threshold at two years, scores were consistently higher for the abiraterone group. Lower scores in the docetaxel group throughout the first year suggests persistent or slow-to-recover treatment-related toxicity. There was no evidence that metastatic status had an effect on QoL scores[17].

NICE and ESMO definitions of high-risk non-metastatic prostate cancer differ from the STAMPEDE study criteria[3,5,6].STAMPEDE high-risk criteria are stricter than NICE or ESMO criteria and therefore patients included in the study would have higher risk disease than stipulated by those guidelines. It may be that STAMPEDE patients would benefit more from additional systemic therapy than those included in NICE or ESMO high risk criteria.

The NMA by Rajwa et al. supports the use of abiraterone in patients who would usually receive combination ADT and radiotherapy, as well as those who would receive docetaxel plus ADT and radiotherapy[14].

The adverse effect profile of abiraterone is notably different to that of docetaxel, with markedly higher rates of neutropenia and febrile neutropenia seen with docetaxel. During the COVID-19 pandemic this was significant, when avoiding drug-related immunosuppression was desirable. The SmPC for abiraterone recommends additional monitoring of liver function[1].

Docetaxel is given to patients who are generally fit and who have no significant comorbidities. Patients for whom docetaxel treatment would not be suitable would receive ADT alone. Suitability for treatment with docetaxel is assessed on an

individual basis; patients who are younger with good performance scores are more likely to be offered upfront docetaxel. It is unclear as to the percentage of patients who would be offered docetaxel, clinical expert opinion ranges from 40% up to 70%.

Cost-effectiveness evidence

Background

A literature search by AWTTC identified a cost-utility analysis of adding abiraterone plus prednisolone to ADT in newly diagnosed, advanced prostate cancer in England (UK)[19]. This model was based on the STAMPEDE study data and is described below. A cost utility analysis of adding docetaxel to ADT in newly diagnosed prostate cancer is also briefly described[20].

Context

The cost-utility analysis aimed to determine the value for money to the NHS of adding abiraterone plus prednisolone to long-term hormone therapy (standard of care) in newly diagnosed advanced prostate cancer[19]. The lifetime costs and quality-adjusted life years (QALYs) were estimated using data from the STAMPEDE study supplemented with literature data where necessary, adjusted for baseline patient and disease characteristics[19].

A lifetime simulation model used had 9 health states with 25 allowed transitions [19]. The health states that covered the trial eligibility criteria were: health state 1 (HS1): patients with non-metastatic prostate cancer and HS2 and HS3: patients with metastatic disease. After treatment failure, patients were considered to be in three castrate-resistant prostate cancer health states (HS4, HS5 and HS7), split according to non-metastatic or metastatic (bone or visceral) disease, and with an extra state (HS6) where skeletal-related events were seen after bone metastasis. Information was collected on deaths – whether these were prostate cancer-related (HS8) or not (HS9)[19].

The lifetime simulation model was a patient-level simulation Markov model, performed in R[19]. The model generated lifetime information on the time that patients spent in each health state, by arm and by subgroup, using a 42-day cycle length and based on survival models calculated from data from the STAMPEDE study. Office for National Statistics life tables were used if the predicted date of death was after the participant's last follow-up. The time horizon was 45 years after randomisation, which likely captured all patients' lifetimes: the mean age of the youngest category of patients was 55 years. Forty simulations generated per patient profile gave stable results in deterministic analyses, and 25 in the probabilistic sensitivity analyses (500 iterations). The probabilistic sensitivity analyses were used to provide points on a cost-effectiveness plane, that were translated onto the cost-effectiveness acceptability curve, and into 95% CIs for costs and QALYs per arm and subgroup. Area-under-the-curve methods were used to calculate QALYs, and future QALY's were discounted at 3.5% per year[19].

Utility scores were calculated from complete responses to trial EQ-5D-3L questionnaires using the standard UK tariff [19]. Incomplete questionnaires were deemed missing and were imputed. Utility was imputed as zero from the date of death[19].

Costs were calculated based on healthcare resource use, using the English NHS perspective, in 2017-2018 prices[19]. Unit costs were obtained from standard sources,

including the BNF, NHS Reference Costs 2017–18 and a published docetaxel CUA (Woods et al 2018) with adjustment to 2017-18 prices where needed. A flat serious adverse event (SAE) cost was calculated using information collected in the STAMPEDE study. Published costs for end-of-life care in prostate cancer were also included (£6,897, adjusted to 2017–18 prices [Round et al 2015]), as well as estimated costs for standard monitoring activities, and stoppage of medications where this implied additional healthcare resources[19].

The base-case cost for abiraterone was the BNF cost: £97.68/day[19]. A threshold analysis explored the impact of using lower prices than that, because the NHS purchases abiraterone at an undisclosed discount[19].

Results

The model predicted overall survival of patients with non-metastatic prostate cancer increased from 12.46 years (ADT-only) to 12.75 years with abiraterone added to ADT treatment[19]. Discounted quality-adjusted survival increased from 6.70 (ADT-only) to 7.03 QALYs with abiraterone added to ADT. The model predicted an increase in failure-free survival for non-metastatic prostate cancer from 8.20 (ADT-only) to 12.14 years with abiraterone and ADT; and discounted quality-adjusted failure-free survival increased from 4.72 (ADT-only) to 6.72 QALYs with abiraterone and ADT[19].

Table 1. Total lifetime per-patient costs and QALYs for patients with non-metastatic prostate cancer[19]

	Abiraterone + prednisolone with ADT	ADT-only	Difference
Lifetime costs	£97,558	£48,736	£48,821
Lifetime QALYs	7.03	6.70	0.33
ICER			**£149,748**
ADT: androgen-deprivation therapy; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year			

Abiraterone was not cost-effective for treating non-metastatic prostate cancer[19]. The incremental cost-effectiveness ratio (ICER) was £149,748/QALY gained in the non-metastatic prostate cancer subgroup, with a 2.4% probability of being cost-effective at the £30,000 threshold. Scenario analyses suggested that abiraterone could be cost-effective in non-metastatic prostate cancer if it was priced below £28 per day. At a price below £11 per day abiraterone could dominate (cost less and provide more QALYs) standard-of-care in non-metastatic disease[19]. [Commercial in confidence text removed].

Woods et al (2018) conducted a cost-effectiveness analysis for the addition of off-label docetaxel to standard of care for treatment of newly-diagnosed hormone-sensitive prostate cancer[20]. For non-metastatic patients, the addition of docetaxel was predicted to be cost saving to the NHS (-£251) and produce more QALYs (0.39) over a patient's lifespan and was estimated to be a dominant treatment. Sensitivity analyses indicated a very high probability (> 99%) that docetaxel is cost-effective in both the metastatic and non-metastatic patients at a threshold of £20,000. Using the BNF list price of docetaxel increased the ICER for treatment of non-metastatic disease from dominant to £10,610 per QALY[20]. This analysis was used by NICE to inform the NG131 recommendations for offering docetaxel as an option for treatment of newly-diagnosed high risk hormone sensitive prostate cancer[5]

Health economic issues
All of the cost effectiveness calculations should be interpreted with caution and there are several caveats which must be considered.

The model used the NHS list price of abiraterone, because the discounted price that the NHS pays for abiraterone is confidential. The patent for abiraterone in the UK will expire in September 2022, so generic versions of abiraterone will enter the market, and are likely to lead to lower prices[19].

Immature data was used from the James et al. 2017 study, more recent mature data has since become available with longer term outcome and survival data[12].

AWTTC used data provided in the Clarke et al cost effectiveness paper to calculate the QoL values associated with abiraterone in non-metastatic patients. The difference in lifetime discounted QoL values was 0.014 in favour of abiraterone with ADT versus ADT alone. Although abiraterone was associated with little difference in discounted QoL values; the analysis demonstrated overall QoL and QALY gains associated with abiraterone, largely driven by the longer duration of failure-free survival[19].

The lifetime model used data with a median study follow-up of around 3 years to extend the model to a 45-year horizon. Only limited information was available for validation of the longer-term predictions by comparison with other published studies[19].

The STAMPEDE data were not complete regarding medications or disease progression events, because complete follow-up post-progression was not mandatory. For the non-metastatic subgroup, the gaps were filled by assuming that outcomes after metastases mimicked those for patients with metastatic prostate cancer[19].

Changes were made to standard-of-care treatment during the STAMPEDE study, so neither arm in the cost-effectiveness analysis exactly replicates current practice in the NHS[19].

The lifetime QALY gains were similar for docetaxel plus ADT versus ADT alone (0.39) and abiraterone plus ADT versus ADT alone (0.33) in the two analyses described[19,20]. Patient characteristics are likely to differ between these two studies with only younger, fitter patients suitable for treatment with docetaxel. There are no cost-effectiveness data directly comparing abiraterone treatment with docetaxel treatment in the treatment of high-risk, non-metastatic, hormone-sensitive prostate cancer. Both NICE and SMC have published redacted cost effectiveness data used in the health technology appraisal of abiraterone for the treatment of high-risk metastatic hormone sensitive prostate cancer. Although the analyses included comparison with docetaxel both used undisclosed discounted prices for abiraterone and was for a different patient population therefore cannot be used as a suitable proxy for the non-metastatic group.

Budget impact

As of 1 October 2022 generic formulations of abiraterone will be available in NHS at a cost of [Commercial in confidence text removed] per pack of 56 tablets (500 mg) excluding VAT. Treatment with abiraterone requires monthly monitoring of blood pressure, serum potassium and fluid retention[1]. The SmPC also recommends that serum transaminases should be monitored every 2 weeks for the first 3 months of starting treatment with abiraterone and then monthly after that[1].

The 2021 prostate cancer national audit showed 2,561 cases of newly diagnosed prostate cancer in Wales during 1 April 2019 to 31 March 2020[4]. Of these, 768 men (32%) had high-risk (as per NICE criteria) or locally advanced disease[4]. A total of 821 men underwent radical radiotherapy[7] clinical experts extrapolate that 32% of all patients undergoing radical radiotherapy (n = 263) would meet high risk criteria (similar to STAMPEDE) and may be eligible to receive abiraterone treatment. Of patients receiving radical radiotherapy 120 men (15%) received radiotherapy to the whole pelvis including lymph nodes (these patients would be node positive or have very high-risk disease and would be eligible to receive abiraterone). Therefore, the numbers of patients in Wales eligible for abiraterone treatment adjuvant to radical radiotherapy, based on clinical expert opinion, is estimated to range from 120 to 263.

Table 2 details the estimated annual cost to NHS Wales of using abiraterone plus prednisolone, and docetaxel. The annual cost of ADT has not been listed as all patients will receive ADT either as SoC or in combination with abiraterone and prednisolone or with docetaxel. Similarly, radiotherapy costs have been excluded from the calculation as the assumption is that all eligible patients would receive this irrespective of future therapies. The medicine acquisition cost for abiraterone is based on the agreed contract price plus VAT at the licensed dose of 1,000 mg daily (two 500 mg tablets). Clinical experts state that patients receiving treatment with abiraterone will start treatment four to six months prior to radiotherapy, in addition to two years treatment post radiotherapy. Costs are therefore provided for three years of treatment in total. We have assumed that, in addition to the standard monitoring received every six months by all patients, a patient treated with abiraterone would have additional blood monitoring for serum transaminases in primary care (13 in year one; 10 in year two; and 5 in year three) and additional fifteen-minute reviews by a registrar or nurse (4 in year one; 2 in year two; and 1 in year three). The medicine acquisition cost and monitoring cost of docetaxel (75 mg/m^2) are based on the national average unit costs for procurement and delivery taken from the 2020-21 National Schedule of Reference Costs for NHS trusts and NHS foundation trusts. Docetaxel is given as six cycles in year one, thereafter patients will be treated with ADT alone.

Table 2. Estimated annual costs for abiraterone and docetaxel per patient receiving ADT in Wales

	Year 1	Year 2	Year 3
Abiraterone (2 x 500 mg tablets)*	¶¶	¶¶	¶¶
Prednisolone (1 x 5 mg tablet)	£10.31	£10.31	£5.16
Annual medicine administration costs	NA	NA	NA
Annual additional monitoring costs†	£234	£166	£83
Annual total cost 1,000 mg/day abiraterone plus 5 mg/day prednisolone¶	¶¶	¶¶	¶¶
Docetaxel (75 mg/m^2; 6 cycles of treatment) §	£2,376.00	£0	£0
Annual medicine administration costs¶	£2,717	£0	£0
Annual additional monitoring costs	NA	NA	NA
Annual total cost of docetaxel¶	**£5,093**	**£0**	**£0**

NA: not applicable
*Confidential NHS Wales contract price plus VAT
¶¶ commercial in confidence figure removed
† Assumes 15-minute appointment with a nurse at GP practice for blood test monitoring (National Cost Collection Data 2019-20, code DAPS 05 Haematology)[21]or non-consultant led medical oncology outpatient appointment for blood monitoring (National Schedule of NHS costs, 2019-20, codes WF01A, DAPS03 and DAPS05[22]) and 13 appointments in year 1, 10 in year 2 and 5 in year 3.
§National average unit cost for procurement of docetaxel taken from 2020-2021 National Schedule of Reference Costs (HRG code SB06Z)
¶2020-2021 National Schedule of Reference Costs: assumes 'Deliver Simple Parenteral Chemotherapy at first attendance' (HRG code SB12Z) for the first dose, followed by 'Deliver Subsequent Elements of a Chemotherapy Cycle' for the other five doses (HRG code SB15Z).

Costs for ADT are not included as these are the same for all treatment options See the relevant Summary of Product Characteristics for the licensed doses and MIMS for the list prices of prednisolone.

Table 3 shows the estimated annual acquisition costs, the patients numbers are given as the median of the estimated range 120 to 263; details of how the patient numbers accrue for each year are shown in appendix 1. Treatment with abiraterone commences up to six months prior to radiotherapy and thereafter for two years, docetaxel is administered as a single course of six cycles following radiotherapy. Standard of care is two years treatment with ADT alone. We have provided three years forecast to capture 30 months of abiraterone treatment. In a scenario without abiraterone clinical experts estimate that between 40% and 70% of patients would be eligible for docetaxel. In Table 3 we have assumed that abiraterone would displace the use of 6 three-weekly cycles of docetaxel in year 1 for 50% of patients and displace ADT alone for the remaining 50% of patients. Scenarios using the lower and higher estimates for patient numbers and docetaxel uptake are provided in

Appendices 2 and 3 respectively. Although abiraterone uptake is expected to be 100% of eligible patients, it has been suggested that up to 10% of patients may opt for treatment with docetaxel; appendix 4 provides the budget impact associated with this scenario.

Table 3. Estimated annual acquisition costs in Wales

	Year 1	Year 2	Year 3
Scenario without abiraterone plus prednisolone			
Number of patients*	193	386	579
Total number of patients receiving intravenous docetaxel (50% uptake)	96	96	96
Number of patients receiving SoC	97	194	194
Scenario with abiraterone plus prednisolone			
Number of patients	193	386	579
Patients receiving abiraterone plus prednisolone	193	386	483
Estimated costs of above scenarios			
Total annual costs without abiraterone plus prednisolone	£488,928	£488,928	£488,928
Total annual costs with abiraterone	¶¶	¶¶	¶¶
Annual net cost	¶¶	¶¶	¶¶

¶¶ commercial in confidence figure removed
ADT: androgen deprivation therapy; SoC: standard of care (ADT alone)
NB. Costs for ADT are not included as these are the same for both treatment options and standard of care

Budget impact issues

We have assumed that abiraterone plus prednisolone oral tablets will displace the use of 6 cycles of intravenous docetaxel, in combination with ADT or ADT alone to treat high-risk, hormone-sensitive prostate cancer. The proportion of patients who would be eligible for docetaxel is unclear and estimates range from 40% to 70%. We have therefore assumed a 50% uptake and sensitivity is provided in appendix 3.

Experts have suggested that, although unlikely, 10% of patients may still opt for treatment with docetaxel, costing for this scenario are provided in Appendix 4.

Although the calculation for patient numbers resulted in a range from 120 to 263, the mean of 193 has been used as the most likely scenario, clinical experts agree that the number is likely to be approximately 200. Costs associated with the lower and upper estimates have been provided in Appendix 2.

The budget impact has not considered the discontinuation of therapy and mortality rates, thus assuming that all patients respond (100% success rate) for up to three years. Clinical experts in Wales have highlighted that the majority of these patients

will remain on treatment for the full two years post radiotherapy, to a total of two years and six months Based on these assumptions patient numbers are expected to remain static from year three onwards.

We've assumed that patients receiving abiraterone would attend 13 appointments in year one, 10 in year two and 5 in year three with a nurse or pharmacist prescriber as a non-consultant outpatient appointment in addition to standard monitoring. This captures the additional monitoring requirements, including a blood tests, in line with SmPC recommendations. This is based on practice in one cancer centre in Wales. Local practice may vary and it may be that additional monitoring may be carried out in primary care by a nurse, phlebotomist or health care assistant which would reduce the monitoring costs considerably.

One cancer centre in Wales anticipates abiraterone to be dispensed and delivered via homecare services. This is estimated to incur an additional cost per patient of [commercial in confidence text removed] in year one, [commercial in confidence text removed] in year two and [commercial in confidence text removed] in year three. However, as medicines provided via homecare provision are exempt from VAT the additional cost is to be [commercial in confidence text removed] in year one and offset in years two and three.

A report published on data from 39 hormone sensitive prostate cancer patients treated with early docetaxel in NHS Wales report a rate of grade 3 and 4 neutropenia of 36% and neutropenic sepsis of 20%[18]. A study by Pulfer et al (2017) calculated the costs associated with docetaxel-related neutropenic sepsis in patients with non-small cell lung cancer in the UK NHS[23]. Microcosting analysis of resource use calculated the mean admission plus treatment cost for an episode of suspected or confirmed neutropenic sepsis to be £4,023 and £5,397 respectively[23]. Clinical experts state that patients would be expected to be admitted to hospital for between two and seven days and treated with intra-venous antibiotics and granulocyte colony-stimulating factor (GCSF).

The most significant adverse effect associated with abiraterone is liver toxicity. Across Phase 3 clinical studies, hepatotoxicity grades 3 and 4 were reported in approximately 6% of patients who received abiraterone acetate, typically during the first 3 months after starting treatment. In trials treatment with abiraterone was stopped until serum transaminases had returned to baseline when treatment could be re-commenced[1]. Treatment interruption is unlikely to be associated with significant costs.

Docetaxel treatment is given as 6 cycles of intravenous administration in a hospital. This is associated with significant clinical resource use, as well as possible increased risk of exposure to COVID-19. Patients receiving docetaxel would be immunocompromised; therefore, the risks associated with contracting COVID-19 would be greater. We have not included these potential costs in our budget impact estimate.

During 2021 and 2022, the Medicines and Healthcare products Regulatory Agency (MHRA) has approved generic versions of abiraterone film-coated tablets (250 mg and 500 mg) made by 12 different pharmaceutical manufacturers. Budget impact calculations have been based on the contract price for NHS Wales.

Additional factors

Prescribing unlicensed medicines

Abiraterone is not licensed to treat this indication and is therefore prescribed 'off label'. Providers should consult relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

Care has been taken to ensure the information is accurate and complete at the time of publication. However, the All Wales Therapeutics and Toxicology Centre (AWTTC) do not make any guarantees to that effect. The information in this document is subject to review and may be updated or withdrawn at any time. AWTTC accept no liability in association with the use of its content. An Equality and Health Impact Assessment (EHIA) has been completed in relation to the One Wales policy and this found there to be a positive impact. Key actions have been identified and these can be found in the One Wales Policy EHIA document.

Information presented in this document can be reproduced using the following citation: All Wales Therapeutics & Toxicology Centre. Evidence Status Report. Abiraterone acetate for the treatment of non-metastatic and locally advanced high-risk, hormone-sensitive prostate cancer (OW20). 2022.

References

1. Janssen-Cilag Ltd. ZYTIGA®500 mg film-coated tablets. Summary of Product Characteristics. Apr 2022 Available at: https://www.medicines.org.uk/emc/product/2381. Accessed Jul 2022.
2. Cancer Research UK. Prostate cancer. Mar 2022. Available at: https://www.cancerresearchuk.org/about-cancer/prostate-cancer. Accessed Jul 2022.
3. James ND, de Bono JS, Spears MR et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *New England Journal of Medicine.* 2017;377:338-351.
4. The National Prostate Cancer Audit (NPCA). NPCA Annual Report 2021. January 2022. Available at: https://www.npca.org.uk/reports/npca-annual-report-2021/. Accessed September 2022.
5. National Institute for Health and Care Excellence. NICE Guideline NG131. Prostate cancer: diagnosis and management. May 2019. Available at: https://www.nice.org.uk/guidance/ng131. Accessed Jul 2022.
6. Parker C, Castro E, Fizazi K et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology.* 2020;31(9):1119-1134.
7. National Cancer Medicines Advisory Group (NCMAG) Programme. NCMAG101 Abiraterone Advice Document. Version 2.0. July 2022. Available at: https://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/ncmag_programme/idoc.ashx?docid=73c2199f-ec79-47a3-ba3f-deef7a9f5eb0&version=-1. Accessed September 2022.
8. National Institute for Health and Care Excellence. Technology Appraisal TA387. Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. Apr 2016. Available at: https://www.nice.org.uk/guidance/ta387. Accessed Jul 2022.
9. National Institute for Health and Care Excellence. Technology Appraisal TA259. Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen. Jun 2012. Available at: https://www.nice.org.uk/guidance/ta259. Accessed Jul 2022.
10. National Institute for Health and Care Excellence. Technology Appraisal TA721. Abiraterone for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer. Aug 2021. Available at: https://www.nice.org.uk/guidance/ta721. Accessed Jul 2022.

11. Scottish Medicines Consortium (SMC). SMC2215. Abiraterone acetate (Zytiga). January 2020. Available at: https://www.scottishmedicines.org.uk/medicines-advice/abiraterone-acetate-zytiga-full-smc2215/. Accessed September 2022.
12. Attard G, Murphy L, Clarke NW et al. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. *Lancet.* 2022;399(10323):447-460.
13. Sydes MR, Spears MR, Mason MD et al. 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):1235-1248.
14. Rajwa P, Pradere B, Gandaglia G et al. Intensification of Systemic Therapy in Addition to Definitive Local Treatment in Nonmetastatic Unfavourable Prostate Cancer: A Systematic Review and Meta-analysis. *European Urology.* 2022;82(1):82-96.
15. Sun G, Zhang X, Chen J et al. What kind of patients with castration-na€ıve prostate cancer can benefit from upfront docetaxel and abiraterone: a systematic review and a network meta-analysis. *Urologic Oncology.* 2018;36:505-517.
16. Wallis CJD, Klaassen Z, Bhindi B et al. Comparison of abiraterone acetate and docetaxel with androgen deprivation therapy in high-risk and metastatic hormone-naïve prostate cancer: a systematic review and network meta-analysis. *European Urology.* 2018;73:834-844.
17. Rush HL, Murphy L, Morgans AK et al. Quality of Life in Men With Prostate Cancer Randomly Allocated to Receive Docetaxel or Abiraterone in the STAMPEDE Trial. *Journal of Clinical Oncology.* 2022;40(8):825-836.
18. Tanguay JS, Catlow C, Smith C et al. High Risk of Neutropenia for Hormone-naive Prostate Cancer Patients Receiving STAMPEDE-style Upfront Docetaxel Chemotherapy in Usual Clinical Practice. *Clin Oncol (R Coll Radiol).* 2016;28(9):611.
19. Clarke CS, Hunter RM, Gabrio A et al. Cost-utility analysis of adding abiraterone acetate plus prednisone/prednisolone to long-term hormone therapy in newly diagnosed advanced prostate cancer in England: Lifetime decision model based on STAMPEDE trial data. *PLoS ONE.* 2022;17(6):e0269192.
20. Woods BS, Sideris E, Sydes MR et al. Addition of Docetaxel to First-line Long-term Hormone Therapy in Prostate Cancer (STAMPEDE): Modelling to Estimate Long-term Survival, Quality-

adjusted Survival, and Cost-effectiveness. *European Urology Oncology.* 2018;1(6):449-458.
21. Personal Social Services Research Unit. II. Community based health care staff, 2021. Available at: https://www.pssru.ac.uk/pub/uc/uc2021/communitybasedhcstaff.pdf. Accessed September 2022.
22. England N. 2019/20 National Cost Collection Data Publication. 2022. Available at: https://www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/. Accessed September 2022.
23. Pulfer A HM, Patel A, Purchase J, Summerhayes M, Newsom-Davis T,. PCN192. Resource Use and Associated Costs of Managing Docetaxel-Related Neutropenic Sepsis in Patients with Advanced Non-Small Cell Lung Cancer in The UK Nhs: Reveal-Ns. *Value in Health.* 2017;20(A399-A811).

Appendix 1
A schematic to show patient number calculations

	Year 1	Year 2	Year 3	
Abiraterone + prednisolone with ADT (100% uptake)			month1-6	month 7-12
Year 1	193	193	193	
Year 2		193	193	193
Year 3			193	193
			579	386
Number of patients	**193**	**386**	**Mean = 483**	
Abiraterone + prednisolone with ADT (90% uptake)				
Year 1	174	174	174	
Year 2		174	174	174
Year 3			174	174
			522	348
Number of patients receiving abiraterone	**174**	**348**	**Mean = 435**	
Number of patients receiving docetaxel (10%)	**19**	**19**	**19**	
Docetaxel with ADT or ADT alone (SoC)				
Docetaxel + ADT (40% uptake)				
Patients receiving docetaxel	**77**	**77**	**77**	
ADT alone (SoC)	**116**	**232**	**232**	
Docetaxel +ADT (50% uptake)				
Patients receiving docetaxel	**96**	**96**	**96**	
ADT alone (SoC)	**97**	**193**	**193**	
Docetaxel +ADT (70% uptake)				
Patients receiving docetaxel	**135**	**135**	**135**	
ADT alone (SoC)	**58**	**116**	**116**	

Appendix 2 Exploratory costs around patient number estimates
Lower patient number estimate

	Year 1	Year 2	Year 3
Scenario without abiraterone plus prednisolone			
Number of patients*	120	240	360
Total number of patients receiving intravenous docetaxel (50% uptake)	60	60	60
Number of patients receiving SoC	60	180	180
Scenario with abiraterone plus prednisolone			
Number of patients	120	240	360
Patients receiving abiraterone plus prednisolone	120	240	300
Estimated costs of above scenarios			
Total annual costs without abiraterone plus prednisolone	£305,580	£305,580	£305,580
Total annual costs with abiraterone	¶¶	¶¶	¶¶
Annual net cost	¶¶	¶¶	¶¶

¶¶ commercial in confidence figure removed
ADT: androgen deprivation therapy; SoC: standard of care (ADT alone)
NB. Costs for ADT are not included as these are the same for both treatment options and standard of care

Upper patient number estimate

	Year 1	Year 2	Year 3
Scenario without abiraterone plus prednisolone			
Number of patients*	263	526	789
Total number of patients receiving intravenous docetaxel (50% uptake)	131	131	131
Number of patients receiving SoC	132	264	264
Scenario with abiraterone plus prednisolone			
Number of patients	263	526	789
Patients receiving abiraterone plus prednisolone	263	526	658
Estimated costs of above scenarios			
Total annual costs without abiraterone plus prednisolone	£667,183	£667,183	£667,183
Total annual costs with abiraterone	¶¶	¶¶	¶¶
Annual net cost	¶¶	¶¶	¶¶

¶¶ commercial in confidence figure removed
ADT: androgen deprivation therapy; SoC: standard of care (ADT alone)
NB. Costs for ADT are not included as these are the same for both treatment options and standard of care

Appendix 3. Exploratory costs around docetaxel uptake estimates
Lower docetaxel uptake estimate (40%)

	Year 1	Year 2	Year 3
Scenario without abiraterone plus prednisolone			
Number of patients*	193	386	579
Total number of patients receiving intravenous docetaxel (40% uptake)	77	77	77
Number of patients receiving SOC	116	232	232
Scenario with abiraterone plus prednisolone			
Number of patients	193	386	579
Patients receiving abiraterone plus prednisolone	193	386	483
Estimated costs of above scenarios			
Total annual costs without abiraterone plus prednisolone	£392,161	£392,161	£392,161
Total annual costs with abiraterone	¶¶	¶¶	¶¶
Annual net cost	¶¶	¶¶	¶¶
¶¶ commercial in confidence figure removed Costs for ADT are not included as these are the same for both treatment options and standard of care			

Upper docetaxel uptake estimate (70%)

	Year 1	Year 2	Year 3
Scenario without abiraterone plus prednisolone			
Number of patients*	193	386	579
Total number of patients receiving intravenous docetaxel (70% uptake)	135	135	135
Number of patients receiving SOC	58	116	116
Scenario with abiraterone plus prednisolone			
Number of patients	193	386	579
Patients receiving abiraterone plus prednisolone	193	386	483
Estimated costs of above scenarios			
Total annual costs without abiraterone plus prednisolone	£687,555	£687,555	£687,555
Total annual costs with abiraterone	¶¶	¶¶	¶¶
Annual net cost	¶¶	¶¶	¶¶
¶¶ commercial in confidence figure removed Costs for ADT are not included as these are the same for both treatment options and standard of care.			

Appendix 4. Exploratory costs of 90% abiraterone uptake

	Year 1	Year 2	Year 3
Scenario without abiraterone plus prednisolone			
Number of patients*	193	386	579
Total number of patients receiving intravenous docetaxel (50% uptake)	96	96	96
Number of patients receiving SoC	97	194	194
Scenario with 90% uptake of abiraterone plus prednisolone			
Number of patients	193	386	483
Patients receiving abiraterone plus prednisolone (90%)	174	348	435
Patients receiving docetaxel (10%)	19	19	19
Estimated costs of above scenarios			
Total annual costs without abiraterone plus prednisolone	£488,928	£488,928	£488,928
Total annual costs with abiraterone	¶¶	¶¶	¶¶
Annual net cost	¶¶	¶¶	¶¶

¶¶ commercial in confidence figure removed
ADT: androgen deprivation therapy; SoC: standard of care (ADT alone)
NB. Costs for ADT are not included as these are the same for both treatment options and standard of care