TAR 399 – Abiraterone Acetate for high-risk hormone naïve and high-risk hormone sensitive metastatic prostate cancer

This assessment provides an estimate of the likely cost-effectiveness range of abiraterone acetate for high risk metastatic hormone naïve/hormone sensitive prostate cancer. Note that this is a rapid analysis - this estimate may need to be further validated with a more detailed cost-utility analysis.

A summary of the proposal is provided in the table below.

PROPOSAL OVERVIEW
Pharmaceutical Abiraterone Acetate (Zytiga) 250mg tablets – 120 per packet.
Supplier Janssen
Proposed Indication High risk hormone naïve and high-risk hormone sensitive metastatic prostate cancer
Dosing 1000mg once daily (4x250mg tablets) abiraterone acetate Used in combination with 5mg prednisone or prednisolone daily
Pharmaceutical Price Product already listed on Pharmaceutical Schedule for another patient group. List price: $4276.19 per pack (120x250mg tablets) Net price (after rebate): s9(2)(b)(ii); per pack (120x250mg tablets) Supplier proposed price in submission s9(2)(b) per pack (120x250mg tablets) Contract signed February 2015 (A764485)
PTAC PRIORITY PTAC November 2018 – Low Priority CaTSoP July 2019 – High priority PTAC November 2019 – endorsed CaTSoPs minutes
PHARMCONNECT REFERENCE

1 Proposal Overview

1.1 Summary

An application for the funding of abiraterone acetate for high risk hormone naïve or hormone sensitive metastatic prostate cancer was received from Janssen in August 2018.

The table below provides a summary of the patient population; intervention; comparator treatment; and main outcomes of treatment.

Table 1: PICO

POPULATION	Patients with newly diagnosed high risk hormone naïve or high-risk hormone sensitivity metastatic prostate cancer. (See special authority below for more detail)
INTERVENTION	Abiraterone Acetate (1000mg tablet once daily) + ADT • Goserelin - 10.8mg subcutaneous injection 3 monthly • Bicalutamide 50mg od + Prednisone/prednisolone (5mg tablet once daily)
COMPARISON	Either 1. ADT in combination with prednisone/prednisolone 2. Docetaxel and ADT in combination with prednisone/prednisolone ADT • Goserelin - 10.8mg subcutaneous injection 3 monthly • Bicalutamide 50mg od + Prednisone/prednisolone (5mg tablet once daily) + Docetaxel (75mg/m^2, 90 minute IV every 2 or 3 weeks)
OUTCOME	Gain in overall survival and metastatic progression free survival.

1.2 Patient Population

Prostate cancer initiates in the prostate, an exocrine gland located at the base of the bladder with a primary function of producing prostate fluid, one of the main components of semen. Androgens are hormones which are responsible for prostate cell growth, proliferation, and differentiation, and also play a significant role in tumorigenesis. The majority of patients with prostate cancer initially respond to androgen deprivation therapy (ADT); however, most develop progressive disease that is resistant to further hormone therapy (castration resistant).

Epidemiology

Prostate cancer is the most commonly diagnosed malignancy in men in New Zealand, with more than 3000 cases diagnosed annually and accounting for more than 600 deaths per year. The primary risk factor for developing prostate cancer is aging, and consequently the majority of cases are diagnosed in men over the age of 60 years. The incidence rate also increases for men who have relatives with the disease.

A recent study conducted in New Zealand identified that 76% of patients are diagnosed with localised disease, 12% with locally advanced disease, and 12% with metastatic prostate cancer (Lao et al. Eur J Cancer Care [Engl]. 2016;25:262-8). The supplier has suggested that 60% of patients with locally advanced disease are high-risk and 90% of patients with metastatic prostate cancer are high-risk. PHARMAC staff were unable to corroborate these estimates.

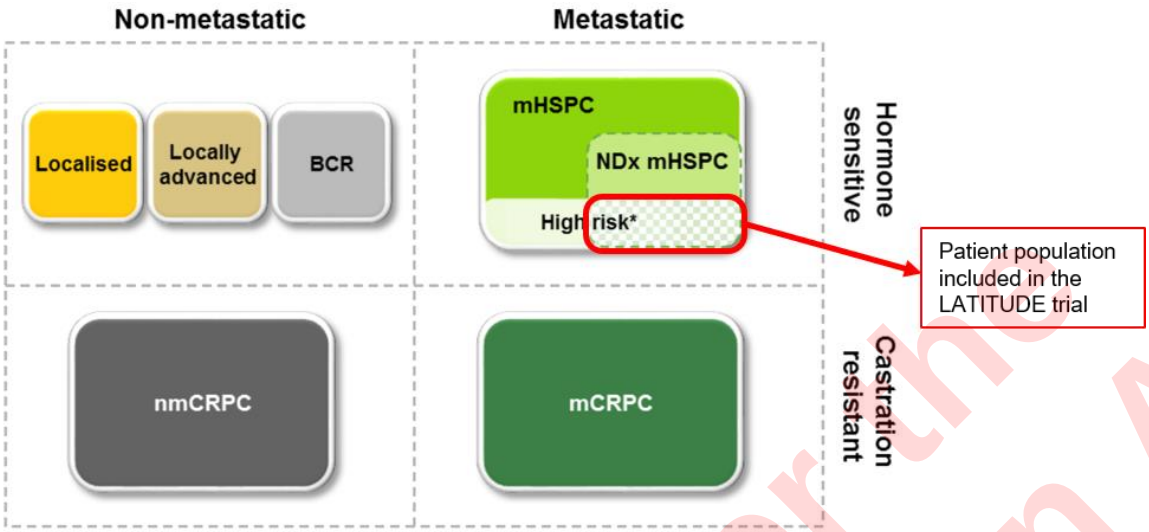
The incidence of prostate cancer in Māori men is 91.8 per 100,000 population compared with 96.3 per 100,000 population for non-Māori men. While the incidence rate is lower, Māori men face a higher mortality rate than non-Māori men (25.1 per 100,000 compared with 17.1 per 100,000). This survival inequity is likely due to Māori men being more likely to have advanced disease at diagnosis (Lao et al. Eur J Cancer Care [Engl]. 2016;25:262-8).

Health need

Prostate cancer is often slow growing, with early stage disease presenting with no symptoms attributable to cancer. Urinary frequency, urgency, nocturia, and hesitancy are commonly observed, but are usually related to concomitant benign prostate enlargement. The most commonly observed symptom of metastatic disease is bone pain, although symptoms vary depending on the site of metastases. Urological complications of metastatic disease can include urethral obstruction, abdominal pain, urinary retention, and dysuria.

Patients who are diagnosed initially with metastatic disease have poor outcomes. An epidemiologic study conducted in New Zealand found that the 5-year survival rate for patients with metastatic disease at diagnosis was 17.6% (Lao et al. Eur J Cancer Care [Engl]. 2016;25:262-8). Based on the results of a number of recent phase 3 clinical trials, the supplier has estimated that the median overall survival (OS) of patients with newly diagnosed high-risk mHSPC receiving ADT is approximately 34 months.

The graphic below was provided by the supplier to describe the different populations within prostate cancer. The area noted in red is the proposal under consideration.



BCR, biochemical recurrence; mCRPC, metastatic castration resistant prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer; NDx, newly diagnosed; nmCRPC, non-metastatic castration resistant prostate cancer.

Hormone-naïve: Patients who have not previously received hormone therapy, or patients who have received up to 3 months of hormone therapy (GnRH agonists or orchiectomy with or without concurrent anti-androgens) but have not become resistant. This is the definition of hormone naïve used in the LATITUDE study protocol, the pivotal trial that supports this application.

Hormone-sensitive: Patients who have not previously received hormone therapy or are continuing to respond to hormone therapy (i.e. are not showing progression). The definition of hormone sensitive includes patients who are hormone naïve.

High-risk: High-risk is a definition specific to the LATITUDE study protocol, the pivotal trial in support of this application. High-risk is defined as patients with at least two of the following prognostic factors:

- Gleason score ≥8;
- ≥3 bone lesions;
- Measurable visceral metastases (excluding lymph node disease).

1.2 Current Treatment in New Zealand

Metastatic prostate cancer is not considered curable. The primary aim of treatment is to provide symptomatic relief and extend survival. There are currently two treatment options available in New Zealand for men with mHNPC or newly diagnosed mHSPC: ADT in combination with docetaxel for patients fit enough to receive chemotherapy, or ADT alone. CaTSoP considered that many patients who are fit enough to receive chemotherapy may not receive it due to the tolerability profile that has a large impact on quality of life in a population who are likely to still be working and living full lives. It is likely that tumour burden is considered by medical oncologists to determine who would benefit from docetaxel chemotherapy.

ADT can include surgical orchiectomy or medical orchiectomy with GnRH agonists (i.e. goserelin), with or without anti-androgens (i.e. bicalutamide, flutamide). The goal of ADT

is to reduce the levels of testosterone and other androgens, which are key drivers of prostate cancer growth. The currently available ADTs decrease androgen production by the testes but do not affect androgen production by other tissues including the adrenal glands and the tumour itself.

1.3 Intervention

Abiraterone acetate is a selective irreversible inhibitor of CYP17A1, which is an enzyme required for androgen biosynthesis in testicular, adrenal, and prostatic tumour tissue. A consequence of inhibiting CYP17A1 is an increase in mineralocorticoid levels; therefore, patients treated with abiraterone acetate also receive prednisone or prednisolone in order to avoid mineralocorticoid toxicities.

Abiraterone acetate has a recommended daily dose of 1000mg taken as a single dose in combination with 5mg once daily of prednisone or prednisolone. Abiraterone acetate should be taken at least two hours after eating and no food should be eaten for at least one hour after. The tablets should be swallowed whole with water.

Medsafe

The New Zealand data sheet for abiraterone acetate can be found here.

Abiraterone in combination with prednisone or prednisolone and androgen deprivation therapy (ADT) is indicated for the treatment of high-risk metastatic hormone naïve prostate cancer (mHNPC) or newly diagnosed high-risk metastatic hormone sensitive prostate cancer (mHSPC).

Abiraterone in combination with prednisone or prednisolone is indicated for the treatment of patients with metastatic castration resistant prostate cancer (mCRPC) who are asymptomatic or mildy symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated and for the treatment of metastatic advanced prostate cancer (mCRPC) who have received prior chemotherapy containing a taxane.

Current funding

Abiraterone acetate has been listed on the Pharmaceutical schedule since 2015 for the treatment of metastatic castration resistant prostate cancer subject to a special authority.

CaTSoP in July 2019 noted that a criterion that stimulates patients cannot have had prior treatment with abiraterone acetate will need to be added to the current special authority criteria to ensure patients are eligible to receive abiraterone acetate only once, either for newly diagnosed high risk mHNPC/mHSPC or for metastatic castration-resistant prostate cancer, as there is a lack of evidence to support a further line of abiraterone treatment following relapse.

Special Authority

The following Special Authority was proposed by CaTSoP at their meeting in July 2019.

Initial application - (hormone-naïve or hormone-sensitive) only from a medical oncologist or radiation oncologist, or any medical practitioner on the recommendation of a medical oncologist or radiation oncologist. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

1. Patient has metastatic prostate cancer documented by a positive bone scan or metastatic lesions on CT or MRI; and
2. Patient was diagnosed with metastatic prostate cancer within the last three months; and
3. Patient does not have neuroendocrine differentiation or small-cell histologic features; and
4. Patient has an ECOG performance score of 0-2; and
5. At least two of the following:
   5.1. Patient has measurable visceral metastases on CT or MRI (excluding nodes); or
   5.2. Patient has three or more lesions by bone scan, CT or MRI; or
   5.3. Patient has a Gleason score of eight or more (International Society of Urological Pathologists [ISUP] Grade 4 or 5); and
6. Any of the following:
   6.1. Patient has not previously received treatment for metastatic prostate cancer; or
   6.2. Patient has received only one course of palliative radiation or surgical therapy to treat symptoms associated with metastatic disease; or
   6.3. Patient has received up to three months of androgen deprivation therapy and is continuing to respond to treatment; and
7. Abiraterone not to be given with taxane chemotherapy.

Renewal application – (hormone-naïve or hormone-sensitive) only from a medical oncologist or radiation oncologist, or any medical practitioner on the recommendation of a medical oncologist or radiation oncologist. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

1. No evidence of clinical disease progression; and
2. No initiation of taxane chemotherapy with abiraterone; and
3. The treatment remains appropriate and the patient is benefitting from treatment

2 Health Benefits (Source: July 2019 CaTSoP paper)

Table 2, Table 3 and Table 4 below outline the key trial evidence for abiraterone acetate for hormone sensitive, high risk, metastatic prostate cancer that was considered by PTAC and CaTSoP.

2.1 Clinical Evidence

Table 2: Summary of evidence from LATITUDE

Trial	Study Design	Patient Group(s)	No. Patients	Intervention	Duration	Primary endpoint: mOS	Primary endpoint: Radiographic mPFS	Safety	Citation
LATITUDE primary publication	Phase 3 Randomised (1:1) Double-blind Placebo-controlled	Newly-diagnosed high-risk mHSPC (including patients with ≤3 months of LHRH or orchiectomy)	N = 1199	ADT + abiraterone acetate 1000 mg + prednisone 5 mg OR ADT + placebo + prednisone 5 mg	30.4 months	NR abiraterone vs 34.7 months placebo (HR 0.62; 95% CI 0.51-0.75; P<0.0001)	33.0 months abiraterone vs 14.8 months placebo (HR 0.47; 95% CI 0.39-0.55; P<0.001)	Grade 3-4 AEs: 63% abiraterone vs 48% placebo AEs leading to treatment discontinuation: 12% abiraterone vs 10% placebo AEs leading to does modification/interruption: 32% abiraterone vs 17% placebo	Fizazi et al. N Engl J med. 2017;377:352-360.
LATITUDE long-term follow-up	Phase 3 Randomised (1:1) Double-blind Placebo-controlled	Newly-diagnosed high-risk mHSPC (including patients with ≤3 months of LHRH or orchiectomy)	N = 1199	ADT + abiraterone acetate 1000 mg + prednisone 5 mg OR ADT + placebo + prednisone 5 mg	41.4 months	NR abiraterone vs 36.7 months placebo (HR 0.64; 95% CI 0.54-0.76; P<0.0001)	Not reported	Grade 3-4 AEs: 66% abiraterone vs 50% placebo AEs leading to treatment discontinuation: 14% abiraterone vs 10% placebo	Fizazi et al. J Clin Oncol 36, 2018 (suppl; abstr 5023).

Table 3: Summary of evidence from LATITUDE – patient reported outcomes

Trial	Study Design	Patient Group(s)	No. Patients	Intervention	Duration	Brief Pain Inventory – Short Form (BPI-SF)	Brief Fatigue Inventory (BFI)	Functional Assessment of Cancer Therapy Prostate scale (FACT-P)	Citation
LATITUDE PROs and HRQoL	Phase 3 Randomised (1:1) Double-blind Placebo-controlled	Newly-diagnosed high-risk mHSPC (including patients with ≤3 months of LHRH or orchiectomy)	N = 1199	ADT + abiraterone acetate 1000 mg + prednisone 5 mg OR ADT + placebo + prednisone 5 mg	30.9 months	Median time to worst pain intensity progression not reached in either group	Median time to worst fatigue intensity was not reached group	Median time to deterioration of functional status by FACT-P total score 12.9 months abiraterone vs 8.3 months placebo	Chi et al. Lancet Oncol. 2018;19:194-206.

Table 4 Summary of evidence from STAMPEDE

Trial	Study Design	Patient Group(s)	No. Patients	Intervention	Duration	Overall survival (OS)	Failure-free survival (FFS)		Citation
STAMPEDE	Phase 2/3 Randomized (1:1) Open-label	Prostate cancer that was newly diagnosed and metastatic, node-positive, or high-risk locally advanced, or previously treated with surgery or radiotherapy and now relapsing with high-grade features (all hormone therapy naïve)	N = 1917	ADT + abiraterone acetate 1000 mg + prednisolone 5 mg OR ADT alone	40 months	184 deaths abiraterone acetate vs 262 ADT-alone 3-year OS: 83% abiraterone acetate vs 76% ADT-alone (HR 0.63; 95% CI 0.52-0.76; *P*<0.001)	248 events abiraterone acetate vs 535 ADT-alone 3-year FFS: 75% abiraterone acetate vs 45% ADT alone (HR 0.29; 95% CI 0.25-0.34; P<0.001)	Grade 3-5 AEs: 47% abiraterone acetate vs 33% ADT-alone	James et al. N Engl J Med. 2017;377:338-351.

2.2 Review of Clinical Evidence

PTAC November 2018

Selected minutes below

Minute 5.3 The Committee recommended that abiraterone acetate in combination with prednisone and androgen deprivation therapy be funded with low priority for the treatment of high-risk metastatic hormone naive prostate cancer (mHNPC) and newly diagnosed high-risk metastatic hormone sensitive prostate cancer (mHSPC) subject to the eligibility criteria for the LATITUDE trial.

Minute 5.4 The Committee recommended that abiraterone acetate for use in combination with prednisone and androgen deprivation therapy in a wider group of patients than those meeting the eligibility criteria for the LATITUDE trial be deferred until additional data regarding use in these settings is available.

Minute 5.5 The Committee recommended that the application for abiraterone acetate for use in combination with prednisone and androgen deprivation therapy for the treatment of high-risk mHNPC and newly diagnosed high-risk metastatic mHSPC be referred to the Cancer Treatment Subcommittee of PTAC for advice regarding the current use of, and benefit of ADT plus docetaxel in the treatment of prostate cancer; appropriate Special Authority criteria for abiraterone (including whether amendment to the current metastatic castration-resistant prostate cancer [mCRPC] criteria would be required); and the potential benefit of abiraterone in a wider group of prostate cancer patients who do not fit the LATITUDE trial eligibility criteria.

CaTSoP July 2019

Selected minutes below

Minute 6.3 The Subcommittee recommended that abiraterone acetate in combination with prednisone or prednisolone and androgen deprivation therapy for the treatment of newly diagnosed high risk metastatic hormone-naïve prostate cancer (mHNPC) and newly diagnosed high-risk metastatic hormone-sensitive prostate cancer (mHSPC) be funded with a high priority subject to a Special Authority criteria.

Minute 6.25: The Subcommittee noted PTAC's recommendation that abiraterone acetate, for use in combination with prednisone and ADT in a wider group of patients than 29 those meeting the eligibility criteria for the LATITUDE trial, be deferred until additional data in these settings is available. The Subcommittee considered that the data from the STAMPEDE trial suggests that there is potential for abiraterone acetate to have health benefits in a population wider than that described by LATITUDE, but agreed that this evidence is not yet mature enough to make a positive recommendation.

Minute 6.29: The Subcommittee considered that the evidence for the efficacy and safety of abiraterone acetate, in combination with prednisone and ADT, for the treatment of newly diagnosed high risk mHNPC and mHSPC provided by LATITUDE, was of moderate to high quality, and that there is a need for an alternative treatment option for these patients. The Subcommittee considered that if abiraterone acetate was to be funded for newly diagnosed high risk mHNPC/mHSPC, that the Special Authority criteria should reflect the eligibility criteria of the LATITUDE trial.

3 PHARMAC Cost-Utility Analysis

A cost-utility analysis (CUA) was undertaken to estimate the cost-effectiveness of abiraterone acetate for high risk hormone naïve and high-risk hormone sensitive metastatic prostate cancer.

3.1 Scope of Analysis

The analysis was undertaken from the perspective of the funder, with regards to PHARMAC's Factors for Consideration.

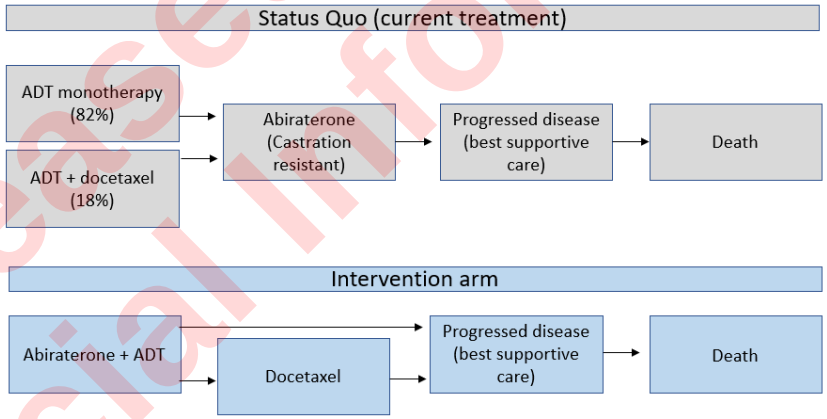
3.1.1 Target Population

The target population for this analysis was defined as patients with high risk hormone naïve and high-risk hormone sensitive metastatic prostate cancer as defined in the following Special Authority Criteria (above).

3.1.2 Intervention/Comparator

Figure 1 below outlines the treatment paradigms modelled in the status quo and intervention arms of this model.

Figure 1: Treatment paradigms modelled in the status quo and intervention arm



ADT: adrogen deprevation therapy

Androgen deprivation therapy in the model base case was assumed to be goserelin with bicalutamide. Sensitivity analysis were conducted where alternative ADT therapies, bicalutamide and flutamide were used was also considered.

3.2 Model Structure

A model was constructed to model the different treatment strategies.

3.2.1 Time Horizon

The time-horizon of the CUA was 15 years. Each Markov cycle was monthly.

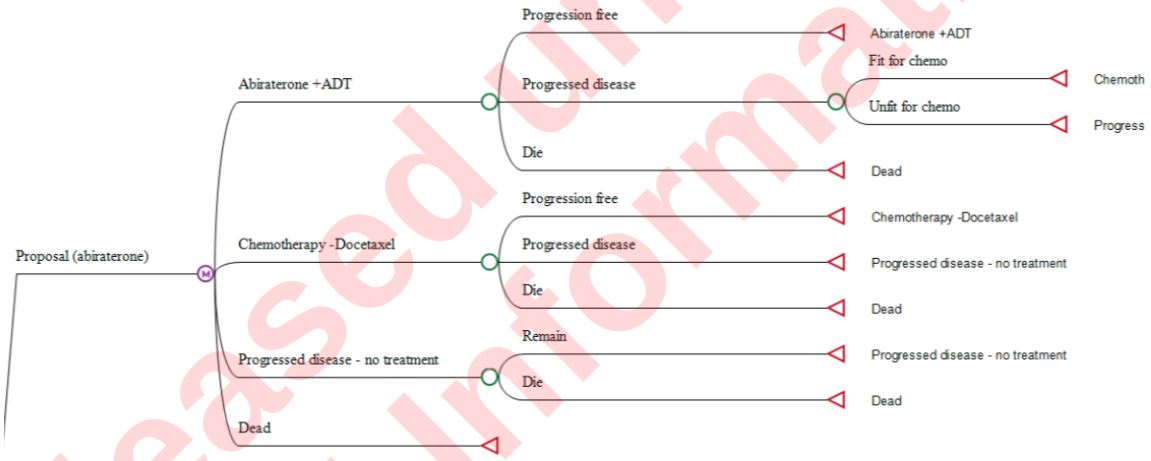
All costs and benefits were discounted at 3.5%.

3.2.2 *Model Structure*

The intervention arm of the model is outlined in Figure 2 below.

The model starts with 100% of the modelled cohort in the abiraterone with ADT treatment health state. With each subsequent cycle, the population in this health state can either remain in this state (reflecting that their disease has not progressed on treatment), experience disease progression or die. Those who experience disease progression and are fit enough to receive docetaxel chemotherapy move to the chemotherapy treatment heath state. They can remain within the chemotherapy treatment health state if their disease does not progress, or move to the progressed disease state upon disease progression or die. Those who are either unfit for chemotherapy following treatment with abiraterone and ADT, or who experience disease progression on docetaxel in the chemotherapy health state move to the progressed disease health state where they remain and receive best supportive care until they die.

Figure 2: Intervention arm of the model

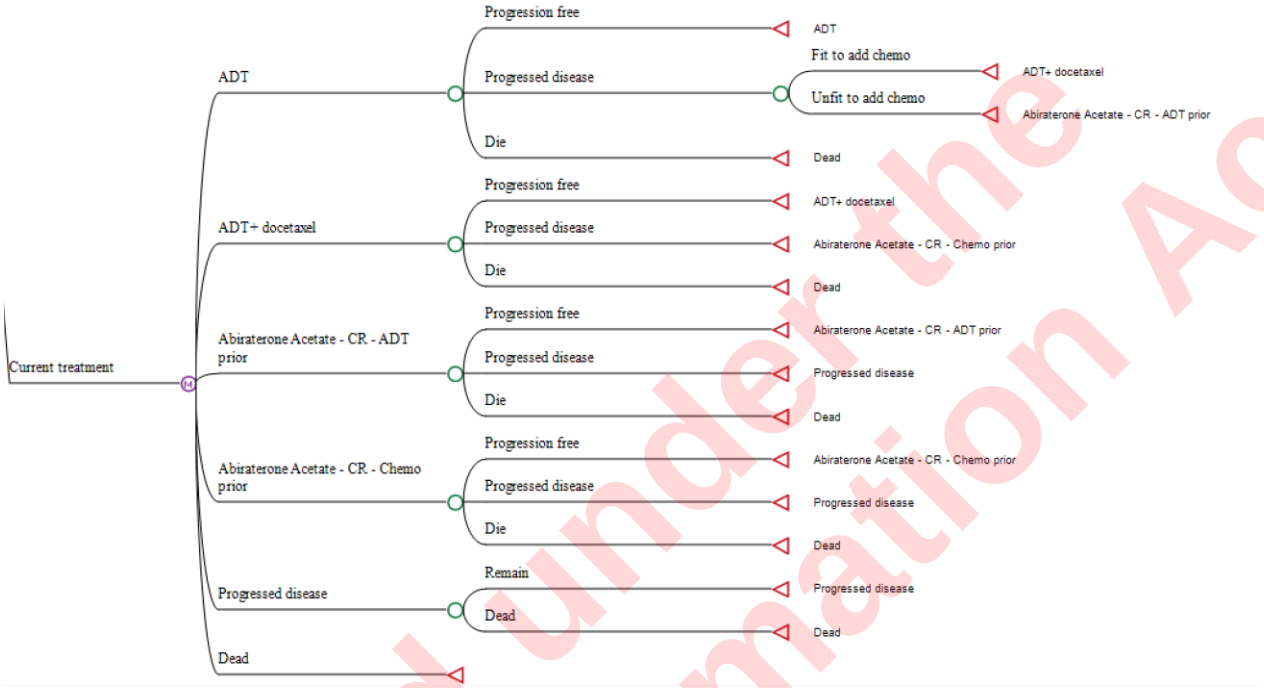


The comparator arm of the model is outlined in Figure 3 below.

At baseline, 82% of the modelled population starts in the ADT treatment health state with the remaining 18% of the population starting in the ADT + docetaxel health state (PHARMhouse data). With each subsequent cycle, there is a chance their disease will progress, and they progress to the next line of treatment, they die or their disease does not progress and they remain in this health state on treatment. The subsequent health states if their disease progresses on ADT or ADT with docetaxel are the two abiraterone treatment states. This part of the treatment paradigm is split into two separate health states to reflect the different clinical effectiveness of abiraterone depending on whether their previous treatment included chemotherapy. From these two treatment states, there is a chance the disease does not progress, and patients remain in this health state, or the disease progresses resulting in movement to a state of progressed disease or death. Once

in the progressed state there is a chance of remaining there on best supportive care or death.

Figure 3: Comparator arm of the model



3.3 Transformation and Extrapolation of Clinical Evidence

Probability of progression and death on abiraterone acetate hormone sensitive, high risk, prostate cancer

Probability of progression (abiraterone, HSmPC)

The probability of progression on abiraterone acetate in the intervention arm of the model was informed by the Kaplan-Meier curve of progression free survival published in the LATTITUDE interim analysis (Fizazi et al, 2017). The first 32 months only were digitised due to low patient numbers as the timeline increased. The data was then fitted with exponentials to determine transition probabilities. The first 4 months were digitised separately to the remaining period to increase the goodness of fit. The monthly probability of progression on abiraterone was estimated to be 0.9% per month in the first 4 months and 2.2% per month thereafter.

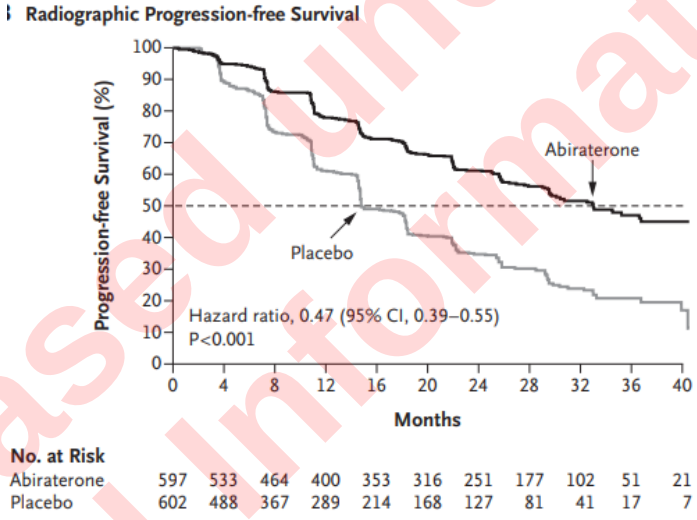


Figure 4: Radiological PFS of abiraterone acetate vs ADT - LATTITUDE Fizazi 2017

Probability of death abiraterone (abiraterone, HSmPC)

The probability of death from abiraterone in the intervention arm of the model was informed by the Kaplan-Meir overall survival curve in the final LATTITUDE analysis published in 2019 by Fizazi et al. Only the first 54 months were digitised. The digitised data were fitted with exponential trend lines to determine transition probabilities. The first 4 months were digitised independently of the remaining months to improve the goodness of fit. The probability of death in the first 6 months was 0.6% per month and 1.5% per month thereafter.

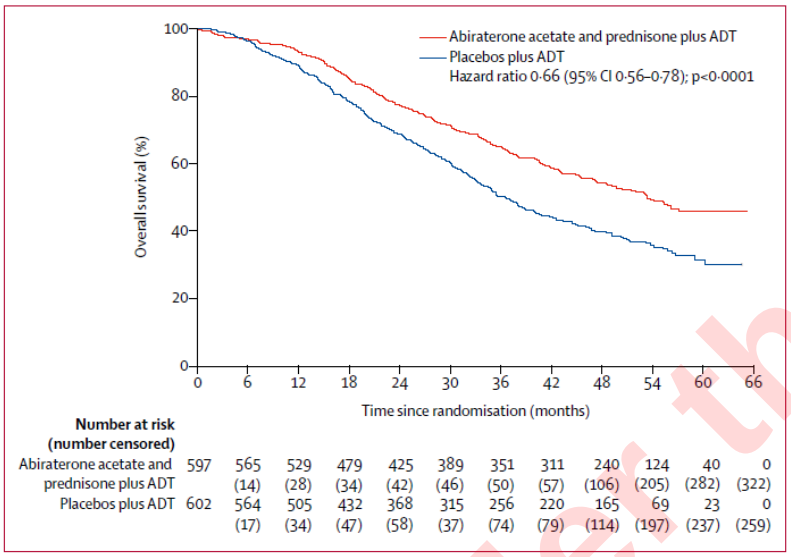


Figure 2: Kaplan-Meier curve of overall survival in the intention-to-treat population
ADT=androgen deprivation therapy.

Figure 5: overall survival of abiraterone acetate vs ADT - LATTITUDE Fizazi 2019

The probability of having docetaxel following abiraterone acetate (intervention arm)

The probability of having docetaxel following abiraterone acetate in the base-case was assumed to be 30%. This was informed by the long term follow up LATTIDUE publication which reported 30% of patients who received abiraterone acetate went on to have subsequent life extending therapies of which the majority had docetaxel.

PHARMAC staff considered that the use of abiraterone acetate after docetaxel could be greater than illustrated in the LATTIDUDE trial as there are currently no other funded treatment options for these patients in New Zealand. A sensitivity analysis was conducted where the probability of receiving subsequent docetaxel was increased to 80%. This model was not sensitivity to this assumption (See Table 13).

The probability of progression and death on docetaxel

The probability of progression while receiving docetaxel with ADT was calculated using the GETUG-AGU 15 trial that compared ADT alone with ADT in combination with docetaxel in non-castrate metastatic prostate cancer (Gravis et al 2013). The first 50 months of data were digitised and plotted with an exponential to determine transition probabilities which were then used to determine a relative risk of progression. The resulting relative risk was 0.77. That is, patients who received ADT in combination with chemotherapy were 0.77 times as likely to progress than those who received ADT alone. The relative risk was then applied to the probability of progression of ADT from the LATTITUDE study to determine the probability of progression from ADT in combination with docetaxel. This resulted in a monthly probability of progression after 4 months of 3.6% (4.7% with ADT alone).

As per the GETUG-AFU trial and advice from CaTSoP (minute 6.21) adding docetaxel did not appear to improve overall survival, so the probability of death was modelled to be the same as ADT alone.

In the absence of other information, the probability of progression on docetaxel was assumed to be the same whether it was taken following abiraterone acetate in the intervention arm (2L) or prior to abiraterone in the comparator arm (1L). The impact of this assumption was tested in sensitivity analyses (See Table 13).

The probability of progression and death on androgen deprivation therapy

The probability of progression and death while on ADT in the comparator arm of the model was determined using a Kaplan-Meir progression curve published in the LATTITUDE trial. The method of determining the transition probabilities is described above. The monthly probability of progression from ADT was calculated to be 0.9% per month in the first 6 months and 4.7% a month thereafter. The monthly probability of death from ADT was calculated to be 0.5% in the first 4 months and 2.2% thereafter.

The probability of starting on ADT or ADT with docetaxel in the comparator arm of the model

The probability of starting the comparator arm of the model in the state of ADT or ADT in combination with docetaxel was informed by Special Authority Data for abiraterone acetate for castration resistant prostate cancer which indicated that 82% of patients who applied for abiraterone acetate had not had prior therapy with a taxane, while the remaining 18% had.

The probability of having docetaxel after ADT comparator arm

The model structure is built to permit a proportion of the cohort who are first treated with ADT alone to have subsequent chemotherapy. In the base-case, 0% are expected to subsequently take chemotherapy on the basis that if they were unfit for chemotherapy at baseline they will not be fit after ADT and that they are better off going straight to abiraterone for which it is known your response will be better if you don't have prior chemotherapy. The impact of this assumption was tested in a sensitivity analysis (See Table 13).

The probability of progression and death on abiraterone acetate – Castration resistant.

In the comparator arm of the model, if disease progression occurs on ADT or ADT with chemotherapy, it is assumed that you are now castration resistant and therefore eligible to receive funded abiraterone. The probabilities of progression and death for these health states were taken from TAR 221 which modelled abiraterone acetate for castration resistant metastatic prostate cancer. This model as well as the model in TAR 221 were

informed by the COU-AA-301 and COU-AA-302 trials which investigate the efficacy of abiraterone with 301 trial patients who have had previous chemotherapy and 302 trial patients who have not had prior chemotherapy.

Similar methods that have been described above were used in TAR 221 to determine transition probabilities from these trials. This is with the exception of the probability of death in the patient population who had not had prior chemo, as this trial was stopped early due to the benefit observed in delaying progression. This transition probability was determined by assessing the relationship between the available survival data and epidemiology data of survival and applying a relative risk to adjust placebo data. For more detail see (TAR 221 - A621640)

A summary of the monthly transition probabilities is shown below – this shows that the probability of progression and death are greater if you have had prior chemotherapy compared to if you have not had prior chemotherapy. This aligns with the fact we are seeing more people commence abiraterone after only having ADT alone as the survival and progression benefits are greater.

Monthly probability	No chemotherapy	Post chemotherapy
Progression	4.2%	11.3%
Death	1.8%	3.8%

Clinical advice received (CaTSoP July 2019) by PHARMAC state that patients should only be able to receive abiraterone acetate once in the treatment of their metastatic disease. Therefore, in this model, patients who receive it while they are hormone sensitive will not be eligible to receive it when they become castration resistant. Abiraterone acetate will continued to be used in the castration resistant setting by those patients who were castration resistant at diagnosis or progression to metastatic disease.

The probability of death from progressed disease

The probability of death from progressed disease was informed by the placebo control arm of CUO-AA-301 which investigated abiraterone acetate compared to placebo in patients with metastatic castration resistant disease post chemotherapy (TAR221). PHARMAC staff considered this a good proxy for the probability of death following several lines of therapy and advancing disease. The materiality of this assumption was tested in the sensitivity analysis (See Table 13).

Summary of transition probabilities.

Table 5 below summaries the transition probabilities discussed above.

Table 5: Summary of model transition probabilities

Probability	Value	Source
Intervention		
Abiraterone + ADT Probability of progression	<4 months: 0.009 >4 months: 0.022	LATTITUDE trial
Abiraterone +ADT Probability of death	<6 months:0.006 >6 months: 0.015	LATTITUDE trial
Chemotherapy Probability of progression	<4 months: 0.007 >4 months: 0.036	LATTITUDE trial * relative risk 0.77 from ADT+ docetaxel vs docetaxel (GETUG_AFU15, Gravis et al 2013)
Chemotherapy Probability of death	<6 months: 0.006 >6 months: 0.022	Same as ADT in LATTITUDE trial No statistically significant difference in overall survival
Probability of death from progressed disease	0.059	TAR 221 (from AA vs placebo trial – Castration resistant)
Comparator		
ADT alone Probability progression	<4 months: 0.009 >4 months: 0.047	LATTITUDE trial
ADT alone Probability of death	<6 months: 0.006 >6 months: 0.022	LATTITUDE trial
ADT with chemotherapy Probability of progression	<4 months: 0.007 >4 months: 0.036	LATTITUDE trial * relative risk 0.77 from ADT + docetaxel vs docetaxel (GETUG_AFU15, Gravis et al 2013)
ADT with chemotherapy Probability of death	<6 months: 0.006 >6 months: 0.022	Same as ADT in LATTITUDE trial No statistically significant difference in overall survival
Abiraterone castration resistant Probability of progression (pre chemotherapy/post chemotherapy)	0.042/0.113	TAR 221
Abiraterone castration resistant Probability of death (pre chemotherapy/post chemotherapy)	0.0188/0.038	TAR 221
Probability of death from progressed disease	0.059	TAR 221 (from AA vs placebo trial – castration resistant)

3.4 Health-Related Quality of Life

Table 6 below outlines the health-related quality of life weights used in the model by health state. Progression free states where no chemotherapy was used were assigned a health-related quality of life of 0.85 while progression free states where chemotherapy was used where assigned a health-related quality of life of 0.63. This reflects the more toxic nature of chemotherapy therapies, and that this toxicity is assumed to resolve if the subsequent treatment state is not chemotherapy-based treatment (i.e. progression from chemotherapy first line to abiraterone to abiraterone once the tumour is castration resistant).

These health utilities were taken from PHARMACs previous economic assessment for abiraterone for castration resistant prostate cancer TAR221. The values were originally derived from publications identified by the supplier and summaries by NICE TA 259.

The sensitivity of the model to these utilities was tested in sensitivity analysis (See Table 13).

Table 6: Summary of health-related quality of life values used in the model

Utility	Health states	HR-QOL
Progression free 1	• Abiraterone + ADT • ADT • Abiraterone Acetate (Castration resistant – ADT prior) • Abiraterone Acetate (Castration resistant – chemotherapy prior)	0.85
Progression free 2 (Chemotherapy)	• Chemotherapy – docetaxel • ADT + docetaxel	0.63
Progressed disease	Progressed disease	0.5

3.5 Costs

3.5.1 Pharmaceutical Cost

Abiraterone Acetate

Abiraterone is taken at a recommended daily dose of 1000mg (4 times 250mg tablets). Abiraterone is already listed on the pharmaceutical scheduled for use in patients with metastatic castration resistant prostate cancer. The supplier has proposed s9(2)(b)(ii); s9(2)(b)(ii); s9(2)(ba)(i)); s9(2)(j)) if funding was widened to include those with high risk castration sensitive prostate cancer. s9(2)(b)(ii)); s9(2)(ba)(i)); s9(2)(b)(ii)); s9(2)(ba)(i)); s9(2)(j)) s9(2)(b)(ii)); s9(2)(ba)(i)); s9(2)(j))

Table 7: Pharmaceutical cost summary – abiraterone acetate

Pharmaceutical	**Abiraterone**
Listed formulation	250mg tablets
Pack size	120 tablets
Price per pack (list)	$4276.19
Net price	s9(2)(b)(ii));
Recommended daily dose	1000mg once daily
Gross cost per dose	$142
Gross cost per month	$4335
Pharmacy margin per month (4%)	$173.42

Androgen deprivation therapy

PHARMAC staff note that commonly used ADT therapies in this setting are goserelin, flutamide and bicalutamide. Table 8 below outlines the costs and relevant doses of each of these.

The base-case model assumes that patients take goserelin three monthly, administered by a GP and 50mg of bicalutamide once daily. Sensitivity analyses where ADT was bicalutamide or flutamide were conducted and resulted in insignificant variation to the base case (See Table 13).

Table 8: Pharmaceutical cost summary – ADT therapies

Pharmaceutical	**Bicalutamide**	**Flutamide**	**Goserelin**
Listed formulation	50mg tabs	250mg tabs	10.8mg syringe
Pack size	28 tablets	84 or 100 tablets	1 syringe
Price per pack (list)	$3.80	$119.50 per 100 $100.38 per 84	$122.37*
Recommended daily dose	50mg once daily	One tablet 3x daily	3-monthly subcutaneous injection

Cost per dose	$0.14	$3.59	$122.37
Cost per month	$4.12	$109.04	$44.20
Administration	Community Pharmacy	Community pharmacy	Health professional (GP)
Pharmacy margin per month (3%)	$0.12	$3.27	-
*Price from 19/20 Tender bid looking to award in March 2020 for October 2020 listing			

Prednisone or prednisolone

The Medsafe datasheet for abiraterone acetate states that abiraterone acetate for HS or HN metastatic prostate cancer is used with 5mg of prednisone or prednisolone while the castration resistant indication requires 10mg daily.

This model assumes that all patients use prednisone tablets as prednisolone liquid is only available in New Zealand for children under the age of 12 and are therefore not part of the eligible population.

Table 9: Pharmaceutical cost summary –Prednisone

Pharmaceutical	**Prednisone**
Formulation	5 mg tab (other formulations available)
Pack size	500 tablets
Dose	5mg once daily (NS/NH) 10mg once daily (CR)
Price per packet	$11.09
Price per tablet	$0.02
Price per month	$0.61 5mg $1.22 10mg
Pharmacy mark-up (3%)	Negligible – not included

Docetaxel

The chemotherapy agent most commonly used in metastatic prostate cancer is docetaxel. Docetaxel is administered over a 90-minute infusion every 2 or 3 weeks at a dose of 75mg/$m^{2.}$

Table 10: Pharmaceutical cost summary –Docetaxel

Pharmaceutical	Docetaxel
Formulation (ECP)	$0.55 per 1 mg
Recommended dose	75mg/m^2 3 weekly, 90-minute infusion
BSA	1.82m^2
Dose	137mg
Cost per dose	$75.10

3.5.3 Health Sector Costs

Cost of administering ADT

Flutamide and bicalutamide are oral tablets that can be prescribed in the community so do not incur an administration cost outside the pharmacy margin.

Goserelin is administered as a subcutaneous injection every 12-weeks. The model assumes that this occurs in a GP clinic at a cost of $80.

Cost of administering Docetaxel

Docetaxel is administered as a 90-minute hospital-based infusion. Table 11 below outlines to cost per infusion included in the model.

Table 11: Administration cost of docetaxel

Variable	Cost	Time (hr)
Bed	$65/hr	1.5
Nurse	$55/hr	1.5
Specialist	$35 per infusion	1
Total	$215	

Cost of disease monitoring

The model base-case included the cost of a quarterly oncologist visit ($362 per visit) in each treatment state (ie all states except progressed disease and death).

Multiple sensitivity analyses were conducted to test the model sensitivity to additional disease management and monitoring costs in a variety of health states and arms of the model (See Table 13).

3.6 Cost-Effectiveness Results

The incremental cost is estimated to be s9(2)(b)(ii); with a QALY gain of 0.74. The estimated QALYs per $1million is therefore s9(2)(b)(ii); s9(2)(ba)(i)); s9(2)(j)). This is shown in the table below.

Table 12: Cost-Effectiveness Results

	Intervention	Comparator	Incremental
QALYs	3.17	2.44	0.74
Cost	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)
QALYs per $1m			

3.7 Sensitivity Analysis

Table 13 below displays the sensitivity analyses run. They illustrate that the model is not highly sensitive to variations in utility.

The likely range is s9(2)(b) QALYs per million. The lower value of this range was informed by the sensitivity analysis where the incremental probability of death between the intervention and comparator arm was halved. The upper value of this range was informed by the sensitivity analysis where the proportion of the cohort who took subsequent chemotherapy was increased from the base case. Within this likely range sensitivity analyses include likely variation in utility values, the probability of death and the cost of monitoring/disease management are represented.

The possible range is s9(2)(b)(ii); QALYs per million. The lower value of this range was informed by the sensitivity analysis where the incremental difference in the probability of progression between the intervention and comparator was increased. The higher value of this range was informed by sensitivity analysis where the incremental probability of progression between the intervention and comparator was decreased and the sensitivity analysis which took in to account a dose intensity of 75%.

Table 13: Sensitivity analyses results

Group	Scenario # (Figure 6)	Analysis	Incremental QALYs	Incremental Costs	Cost per QALY	QALY/$m
	1	**Base case**	**0.74**	s9(2)(b)(ii); s9(2)	s9(2)(b)(ii); s9(2)	s9(2)
Probabilities	2	Proportion eligible for chemotherapy post abiraterone (IA) - 80% vs 30% in base case	0.87	s9(2)(b)(ii); s9(2)	s9(2)(b)(ii); s9(2)	s9(2)
	3	Probability of progression docetaxel IA*2	0.70	s9(2)(b)(ii); s9(2)	s9(2)(b)(ii); s9(2)	s9(2)
	4	Probability of progression docetaxel IA *4	0.68	s9(2)(b)(ii); s9(2)	s9(2)(b)(ii); s9(2)	s9(2)
	5	Probability of progression docetaxel IA *2 + increase in chemo eligibility post abiraterone (IA)	0.77	s9(2)(b)(ii); s9(2)	s9(2)(b)(ii); s9(2)	s9(2)
	6	Probability of progression and death docetaxel IA *2	0.81	s9(2)(b)(ii); s9(2)	s9(2)(b)(ii); s9(2)	s9(2)
	7	Probability of progression abiraterone IA (half the progression difference between AA and ADT+DOCE)	1.43	s9(2)(b)(ii); s9(2)	s9(2)(b)(ii); s9(2)	s9(2)
	8	Probability of progression abiraterone IA (double the progression difference between AA and ADT + docetaxel)	0.31	s9(2)(b)(ii); s9(2)	s9(2)(b)(ii); s9(2)	s9(2)
	9	Probability of death abiraterone IA (double the progression difference between AA and ADT+DOCE)	0.60	s9(2)(b)(ii); s9(2)	s9(2)(b)(ii); s9(2)	s9(2)
	10	Probability of death abiraterone IA (half the progression difference between AA and ADT+DOCE)	0.84	s9(2)(b)(ii); s9(2)	s9(2)(b)(ii); s9(2)	s9(2)
	11	Probability of progressed disease (IA and CA) + 0.1	0.75	s9(2)(b)(ii); s9(2)	s9(2)(b)(ii); s9(2)	s9(2)
	12	Probability of progressed disease (IA and CA) -0.01	0.73	s9(2)(b)(ii); s9(2)	s9(2)(b)(ii); s9(2)	s9(2)
	13	Probability of progressed disease IA +0.1	0.64	s9(2)(b)(ii); s9(2)	s9(2)(b)(ii); s9(2)	s9(2)
	14	Probability of progressed disease IA -0.01	0.77	s9(2)(b)(ii); s9(2)	s9(2)(b)(ii); s9(2)	s9(2)
Utilities	15	Double the utility difference between PFS Chemo and PFS	0.71	s9(2)(b)(ii); s9(2)	s9(2)(b)(ii); s9(2)	s9(2)
	16	Half the utility difference between PFS Chemo and PFS	0.76	s9(2)(b)(ii); s9(2)	s9(2)(b)(ii); s9(2)	s9(2)
	17	Double the difference between PFS and PD	0.73	s9(2)(b)(ii); s9(2)	s9(2)(b)(ii); s9(2)	s9(2)
	18	Half the utility difference between PFS and PD	0.74	s9(2)(b)(ii); s9(2)	s9(2)(b)(ii); s9(2)	s9(2)
Cos t	19	Dose intensity abiraterone (75% of the list and net price)	0.74	s9(2)(b)(ii); s9(2)	s9(2)(b)(ii); s9(2)	s9(2)
	20	Monitoring/management cost of abiraterone (IA and CA) - $50 a month	0.74	s9(2)(b)(ii); s9(2)	s9(2)(b)(ii); s9(2)	s9(2)

	21	Monitoring/management cost of abiraterone (IA and CA)- $500 a month	0.74	s9(2)(b)(ii)); s9(2)	s9(2)(b)(ii)); s9(2)(ba)	s9(2)
	22	Monitoring/management cost of docetaxel (IA and CA) - $500 a month	0.74	s9(2)(b)(ii)); s9(2)	s9(2)(b)(ii)); s9(2)(ba)	s9(2)
Other	23	Relative risk ADT/DOCE vs ADT + 0.1	0.74	s9(2)(b)(ii)); s9(2)	s9(2)(b)(ii)); s9(2)(ba)	s9(2)
	24	Relative risk ADT/DOCE vs ADT - 0.1	0.73	s9(2)(b)(ii)); s9(2)	s9(2)(b)(ii)); s9(2)(ba)	s9(2)
	25	Proportion of people taking ADT + chemo first line in CA - 50% instead of 18%	0.97	s9(2)(b)(ii)); s9(2)	s9(2)(b)(ii)); s9(2)(ba)	s9(2)
	26	10 year time horizon	0.63	s9(2)(b)(ii)); s9(2)	s9(2)(b)(ii)); s9(2)(ba)	s9(2)
	27	5 year time horizon	0.32	s9(2)(b)(ii)); s9(2)	s9(2)(b)(ii)); s9(2)(ba)	s9(2)
	28	0% discount rate	0.91	s9(2)(b)(ii)); s9(2)	s9(2)(b)(ii)); s9(2)(ba)	s9(2)
	29	5% discount rate	0.68	s9(2)(b)(ii)); s9(2)	s9(2)(b)(ii)); s9(2)(ba)	s9(2)
	30	Proportion of people taking chemotherapy 2L CA following ADT monotherapy (20% instead of 0%)	0.75	s9(2)(b)(ii)); s9(2)	s9(2)(b)(ii)); s9(2)(ba)	s9(2)
	31	If ADT therapy was bicalutamide monotherapy (3* daily dose, clinical advice)	0.74	s9(2)(b)(ii)); s9(2)	s9(2)(b)(ii)); s9(2)(ba)	s9(2)
	32	If ADT therapy was flutamide only	0.74	s9(2)(b)(ii)); s9(2)	s9(2)(b)(ii)); s9(2)(ba)	s9(2)
	33	If ADT therapy was goserelin only	0.74	s9(2)(b)(ii)); s9(2)	s9(2)(b)(ii)); s9(2)(ba)	s9(2)

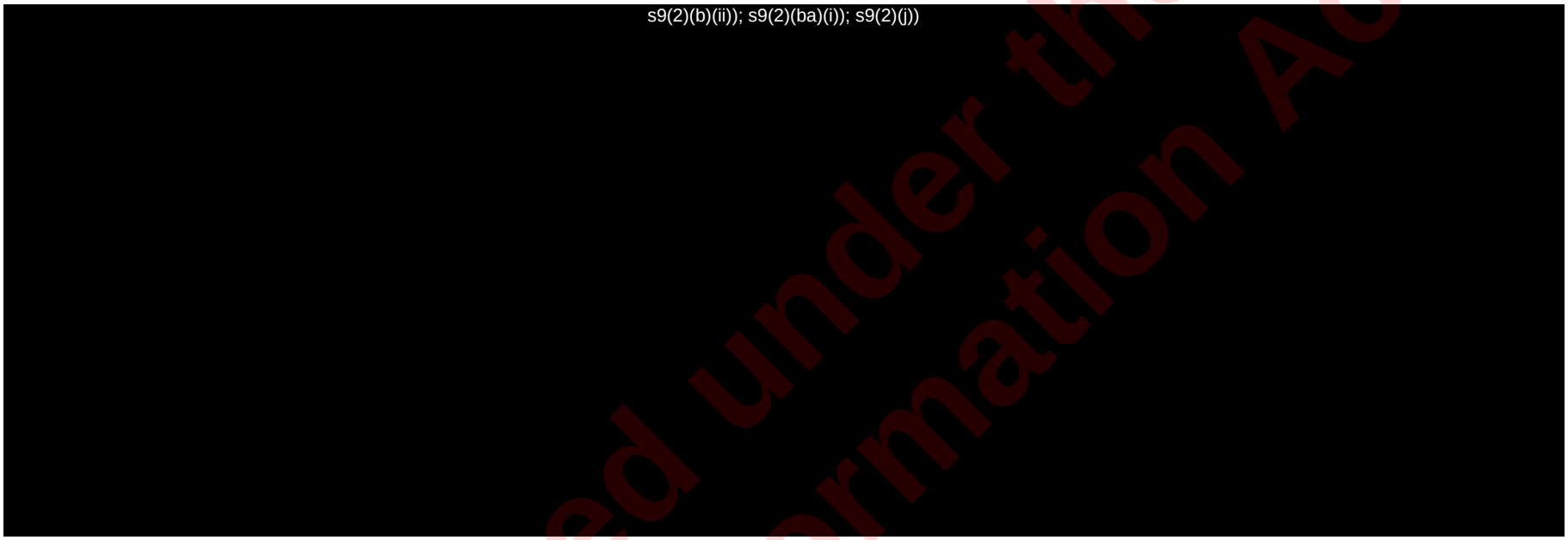


Figure 6: Graph of model sensitivity analyses

Figure notes:

- Black horizontal line indicates the model base-case result
- Yellow box indicates likely cost-effectiveness range
- Grey box indicates possible cost-effectiveness range.
- Scenario analysis numbers on the x-axis refers to scenario analysis listed in Table 13

4 Budget Impact Analysis

The BIA (Table 14) estimates that funding abiraterone will cost an additional s9(2)(b)(ii); s9(2)(ba)(i)); s9(2)(i)) to the CPB in year 1, increasing to s9(2)(b)(ii); s9(2)(ba)(i)); s9(2)(i)) in year 5 with a 5-year NPV (8% discount rate) of s9(2)(b)(ii); s9(2)(ba)(i)); s9(2)(i)).

The BIA estimates that funding abiraterone for this patient population will result in a saving of $0.02 million to the DHB each year, resulting in a 5-year NPV (8% discount rate) of -$0.08 million. This is a result of less docetaxel use.

The BIA uses is a monthly model.

Patient numbers

- CaTSoP (July 2019), restricting patient eligibility to that specified in LATTITUDE trial, considered there would be demand for approximately 110 patients in year 1 increasing to 520 in year five.
- We used the figure of 520 patients in year 5 to reverse calculate the incident population using the Markov trace from the CUA – as outlined in the BIA.
- This results in the following aggregated patient numbers:

Number of patients treated with Abiraterone at the end of each year.					
Year	**1**	**2**	**3**	**4**	**5**
Patient numbers	166	295	394	470	528

Costs

- All dosage and costs were as outlined in the cost-utility analysis above.
- The CPB expenditure considers the incremental change in pharmaceutical cost between abiraterone, ADT and docetaxel between the intervention treatment regimen and the status quo treatment regimen. Note, this does include consideration of abiraterone being used earlier in the treatment paradigm meaning patients can no longer get it later, as current funding restrictions permit.
- The DHB expenditure considers the incremental change in DHB costs associated with the cost of docetaxel infusion and pharmacy margins between the intervention treatment arm and the comparator treatment arm. Costs were as outlined in the cost-utility analysis above.
- Cost-offsets of current second line chemotherapy have not been included as the use of these is delayed but not omitted and their cost is likely not material.

Table 14: Budget impact for Abiraterone Acetate for hormone sensitive metastatic prostate cancer

Year		1	2	3	4	5	5-Year NPV (8% discount rate)
Number of patients on treatment at the end of each year		166	295	394	470	528	-
Intervention	**CPB** ($millions)	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);
	DHB ($millions)	$0.05	$0.14	$0.21	$0.28	$0.33	$0.82
Comparator	**CPB** ($millions)	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);
	DHB ($millions)	$0.07	$0.17	$0.25	$0.30	$0.34	$0.94
Incremental	**CPB** ($millions)	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);	s9(2)(b)(ii);
	DHB ($millions)	-$0.02	-$0.04	-$0.04	-$0.03	-$0.01	-$0.12