HIGHLY CONFIDENTIAL

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Apalutamide for treating prostate cancer [ID1534]

Appraisal Committee Meeting – 7 July 2021
3rd Committee meeting

The following documents are made available to the Committee:

1. **Appraisal Consultation Document (ACD)** as issued to consultees and commentators

2. **Comments on the Appraisal Consultation Document from Janssen**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Prostate Cancer UK

4. **Comments on the ACD received through the NICE website**
   - British Uro-Oncology Group (BUG)

5. **Evidence Review Group critique of company comments on the ACD**

Appraisal Committee Meeting presentation slides – to follow

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Apalutamide with androgen deprivation therapy for treating prostate cancer

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using apalutamide in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: May 2021

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using apalutamide in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 11 June 2021

Next appraisal committee meeting: To be confirmed

Details of membership of the appraisal committee are given in section 5

Issue date: May 2021

1 Recommendations

1.1 Apalutamide plus androgen deprivation therapy (ADT) is not recommended, within its marketing authorisation, for treating prostate cancer in adults who have:

- hormone-relapsed non-metastatic disease at high risk of metastasising
- hormone-sensitive metastatic disease.

1.2 This recommendation is not intended to affect treatment with apalutamide plus ADT that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

This appraisal considers apalutamide for:

- Non-metastatic prostate cancer that has stopped responding to hormone therapy (hormone relapsed) – this is usually treated with ADT alone or with darolutamide plus ADT.
- Hormone-sensitive metastatic prostate cancer – this is usually treated with docetaxel plus ADT if people can have docetaxel, or ADT alone if people cannot have docetaxel.

Clinical trial evidence suggests that, compared with placebo plus ADT, apalutamide plus ADT increases the time until the disease progresses and how long people live. But this evidence is uncertain because in the trials some people could switch from placebo plus ADT to apalutamide plus ADT. Also, some people could have treatments not available in the NHS.

Some of the assumptions in the economic modelling are also uncertain, including the time until the disease progresses and how long people live. The cost-effectiveness estimates are uncertain and higher than what NICE considers an acceptable use of

Issue date: May 2021

NHS resources. Therefore, apalutamide plus ADT is not recommended for hormone-relapsed non-metastatic prostate cancer, or for hormone-sensitive metastatic prostate cancer.

2 Information about apalutamide

Marketing authorisation indication

2.1 Apalutamide (Erleada, Janssen) is indicated:

- 'in adult men for the treatment of non-metastatic castration-resistant prostate cancer in adults who are at high risk of developing metastatic disease
- in adult men for the treatment of metastatic hormone-sensitive prostate cancer in combination with androgen deprivation therapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The price for apalutamide is £2,735 per pack of 112 tablets, each containing 60 mg of the active ingredient (excluding VAT; BNF online, March 2021). The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee considered evidence submitted by Janssen, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

Treatment pathway

Only 1 newer androgen receptor inhibitor would be used in the prostate cancer treatment pathway

3.1 People have a treatment until disease progression or until they can no longer tolerate it. NICE recommends the newer (second generation) androgen receptor inhibitors enzalutamide, abiraterone and darolutamide for treating either metastatic or hormone-relapsed non-metastatic prostate cancer at multiple positions in the treatment pathway:

- NICE's technology appraisal guidance on abiraterone for hormone-relapsed metastatic prostate cancer previously treated with a docetaxel-containing regimen
- Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen
- Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated
- Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated and
- Darolutamide with androgen deprivation therapy for treating hormone-relapsed non-metastatic prostate cancer.

Apalutamide is also a second generation androgen receptor inhibitor. The Cancer Drugs Fund clinical lead explained that a person will have only one of these drugs in the NHS prostate cancer treatment pathway. The clinical experts confirmed that this is because of the similar way the drugs work, and probable resistance to drugs in the same group when used subsequently. For example, if prostate cancer metastasises on apalutamide, it would be expected to be resistant to subsequent treatment with enzalutamide or abiraterone. The Cancer Drugs Fund clinical lead confirmed that NHS England would not commission enzalutamide or abiraterone after apalutamide if it were recommended.

Issue date: May 2021

The committee concluded that only 1 newer androgen receptor inhibitor would be used in the prostate cancer treatment pathway.

There is greater unmet need for hormone-sensitive metastatic prostate cancer than for hormone-resistant non-metastatic cancer

3.2 Until recently, treatment for hormone-relapsed non-metastatic prostate cancer involved continuing androgen deprivation therapy (ADT), even though the cancer may no longer respond to it. However, since NICE recommended darolutamide, there is no longer an unmet need for a new oral treatment at this stage in the pathway (see section **Error! Reference source not found.**~~**Error! Reference source not found.**~~3.4). But another option would add choice and value for patients and their clinicians. Treatment for hormone-sensitive metastatic prostate cancer includes ADT or chemotherapy (docetaxel). People cannot progress from hormone-relapsed non-metastatic disease to hormone-sensitive metastatic disease, or vice versa. So taking apalutamide for 1 indication would not affect the other indication and people would not have to choose when to take apalutamide. A clinical expert explained that people do not need to have a corticosteroid with apalutamide, unlike with some of the other available treatments, so would likely have fewer adverse effects. The committee concluded that although people would value another treatment option at this stage in the pathway, there is greater unmet need for an oral treatment for hormone-sensitive metastatic disease.

Clinical management of hormone-relapsed non-metastatic disease

Treatment aims to delay metastasis

3.3 Once cancer stops responding to ADT it is hormone-relapsed. Apalutamide plus ADT is indicated for treating hormone-relapsed prostate cancer that is at high risk of metastasising. SPARTAN, the trial that informed apalutamide's marketing authorisation (see section 3.6), defined high risk as a blood prostate specific antigen level of 2 nanograms per millilitre or more that has doubled in 10 months. This is the same

indication appraised in NICE's technology appraisal guidance on enzalutamide and on darolutamide. But enzalutamide is not recommended for this population, and darolutamide was not routinely available in the NHS at the start of this appraisal. So darolutamide was not considered a relevant comparator for decision making. Treatment aims to delay metastatic disease, which is associated with reduced quality of life and survival. The patient experts explained that anxiety about cancer metastasising causes psychological distress, which adds to debilitating symptoms such as fatigue, pain, and urinary and bowel problems. The committee concluded that treating hormone-relapsed non-metastatic prostate cancer aims to delay metastasis.

Clinical management of hormone-sensitive metastatic disease

People would welcome the option of treatment with apalutamide plus ADT

3.4 The clinical experts explained that, in clinical practice, people with newly diagnosed hormone-sensitive metastatic prostate cancer have ADT alone or docetaxel plus the oral corticosteroid prednisolone plus ADT. This is in line with NICE's guideline on prostate cancer. Docetaxel is not licensed for hormone-sensitive metastatic prostate cancer, but NHS England commissions it for up to 6 cycles. It is administered as a 1-hour infusion every 3 weeks, with twice daily oral prednisolone 5 mg. People who have had docetaxel plus ADT for hormone-sensitive metastatic disease can have it again once their cancer metastasises. NHS England's interim guidance on treatment options during the COVID-19 pandemic allows use of enzalutamide plus ADT instead of docetaxel plus ADT, or abiraterone with prednisone or prednisolone plus ADT for people who are unable to tolerate enzalutamide. The patient experts explained that people who are diagnosed with metastatic disease may have no or few symptoms. They also explained that some people think that docetaxel worsens quality of life and so choose to have ADT alone, even though the long-term outcomes may be worse. Apalutamide plus ADT is generally better

tolerated than docetaxel plus ADT and is likely to be more effective than ADT alone (see sections 3.15 and 3.20). The committee concluded that people with hormone-sensitive metastatic prostate cancer would welcome the option of treatment with apalutamide plus ADT.

Scope of the appraisal

The committee consider the clinical and cost effectiveness of apalutamide plus ADT across its marketing authorisation

3.5 For hormone-sensitive metastatic prostate cancer, the company proposed apalutamide plus ADT as an alternative to ADT alone or docetaxel plus ADT. It also presented data for the group of people who have ADT alone. That is, people who are not well enough or who cannot tolerate docetaxel, or who choose not to have it because of the adverse events associated with chemotherapy. The Cancer Drugs Fund clinical lead noted that in NICE's technology appraisal on abiraterone for newly diagnosed high-risk hormone-sensitive metastatic prostate cancer (in development) around two-thirds of people with hormone-sensitive metastatic prostate cancer in England have ADT alone. The committee recognised that there are 2 distinct populations who do not have docetaxel plus ADT:

- **People who cannot or should not have docetaxel:** The contraindications to docetaxel include severe prior hypersensitivity to taxanes. NHS England's commissioning policy indicates that contraindications include a poor overall performance status (World Health Organization [WHO] performance status 3 to 4), pre-existing peripheral neuropathy, poor bone marrow function or a life-limiting illness. The policy also states that docetaxel should be used with caution in people with a WHO performance status of 2. People over 70 years are disproportionately represented among people who cannot have docetaxel. Also, TITAN, the key clinical trial of apalutamide plus ADT for this indication (see section 3.14), included only people who were relatively well, with an Eastern Cooperative Oncology Group

status performance status of 0 or 1. The committee was not presented with evidence of apalutamide plus ADT's effectiveness in people who cannot have docetaxel. The company suggested that because people who cannot have docetaxel represent most of the people with hormone-sensitive metastatic prostate cancer, the efficacy results for apalutamide plus ADT from TITAN were relevant for this population.

- **People who choose not to have docetaxel:** Most of these people want to avoid the adverse events associated with docetaxel. The company explained that this includes people with 'low-volume and low-risk' disease, who would have docetaxel at a later stage if they are well enough. The company claimed that this group is younger and has a better prognosis than people with hormone-sensitive metastatic prostate cancer who can have docetaxel. The company did not present evidence of apalutamide plus ADT's effectiveness in people with low-volume and low-risk disease.

The committee agreed that in NHS practice there are some people who cannot, should not or choose not to have docetaxel. NHS England's commissioning policy on docetaxel helps to identify these people. The committee concluded that it would first consider the clinical and cost effectiveness of apalutamide plus ADT within its full marketing authorisation. However, if it was not cost effective for the full population, then it would consider the people who can have docetaxel, and those who cannot, should not, or choose not to have docetaxel.

Clinical evidence for hormone-relapsed non-metastatic disease

The SPARTAN results are in line with planned analyses

3.6 SPARTAN was a phase 3, randomised, multicentre trial comparing apalutamide plus ADT (n=806) with placebo plus ADT (n=401) for hormone-relapsed non-metastatic prostate cancer. The committee considered that the people in SPARTAN reflected people in UK clinical practice reasonably well. The primary endpoint of SPARTAN was

metastases-free survival, that is, the time from randomisation to confirmed evidence of metastasis or death from any cause. Secondary outcomes included overall survival. Exploratory outcomes included time to progression-free survival on first subsequent treatment (PFS2) and health-related quality of life, measured using the EQ-5D questionnaire and the Functional Assessment of Cancer Therapy Prostate Module (FACT-P). PFS2 measures the time from disease progression to the next disease progression on the treatment that follows the trial treatment. The committee was aware that although PFS2 and EQ-5D were exploratory endpoints, the company used them in its cost-effectiveness modelling. The final analysis for metastases-free survival and interim analyses for overall survival and PFS2 were done in May 2017. At this time, most people's cancer had metastasised and the metastases-free survival endpoint had been met. In May 2017, the trial was unblinded and people who had placebo plus ADT could cross over to have apalutamide plus ADT if their cancer had not metastasised. The final analyses of overall survival and PFS2 were done in February 2020. After progression to metastatic disease, people could have abiraterone or enzalutamide as subsequent treatment, as well as other treatments (see section 3.1). The committee concluded that the results were in line with the trial's planned analyses.

In SPARTAN, apalutamide plus ADT is clinically effective compared with placebo plus ADT

3.7 In SPARTAN:

- median metastases-free survival on apalutamide plus ADT was 40.5 months and on placebo plus ADT it was 15.7 months (hazard ratio [HR] 0.30, 95% confidence interval [CI] 0.24 to 0.36)
- median overall survival on apalutamide plus ADT was 73.9 months and on placebo plus ADT it was 59.9 months (HR 0.78, 95% CI 0.64 to 0.96)

- median PFS2 on apalutamide plus ADT was 55.6 months and on placebo plus ADT it was 41.2 months (HR 0.57, 95% CI 0.47 to 0.68).
- mean change in EQ-5D-3L visual analogue score showed statistically significant improvements in the apalutamide plus ADT arm compared with the placebo plus ADT arm at cycles 21 (mean difference 3.03) and 25 (mean difference 3.28), $p<0.05$.

The committee concluded that apalutamide plus ADT extended metastases-free survival, overall survival, PFS2 and health-related quality of life when compared with placebo plus ADT and was clinically effective.

The company should explore methods to adjust for treatment switching other than the modified RPSFTM

3.8 There were 2 reasons to adjust the overall survival and PFS2 hazard ratios reported in SPARTAN for treatment switching because:

- people randomised to placebo plus ADT crossed over to apalutamide plus ADT
- people randomised to apalutamide went on to have abiraterone or enzalutamide.

The committee discussed both situations. In SPARTAN, 76 people (19.0%) randomised to placebo plus ADT crossed over to apalutamide plus ADT. The company explained that this could potentially underestimate the relative benefit of apalutamide plus ADT for overall survival and PFS2. This was because some people reached these endpoints only after the trial was unblinded (see section 3.63.63.6). However, the committee recognised that people could have abiraterone and enzalutamide as subsequent treatments when their disease had metastasised. This would mean that the trial endpoints may not need to be adjusted. The committee also recognised that, in the NHS, people can have only 1 newer androgen receptor inhibitor in the prostate

cancer treatment pathway (see section 3.13~~3~~.13.1~~)~~). Because more people randomised to apalutamide had a second newer androgen receptor inhibitor, the trial results may have overestimated apalutamide plus ADT's apparent effectiveness on PFS2 and overall survival. The number of people who had a second newer androgen receptor inhibitor is academic-in-confidence and cannot be reported here. The clinical expert explained that having a second newer androgen receptor inhibitor is unlikely to extend life, but might be associated with adverse effects. The committee appreciated that this was another reason to adjust for treatment switching. The company considered several different methods to adjust for treatment switching. These included the rank preserving structural failure time model (RPSFTM), iterative parameter estimation (IPE), inverse probability of censoring weights (IPCW) and 2-stage estimation. The company chose to use a 'modified' version of the RPSFTM (Diels et al. 2019) to adjust simultaneously for the effects of treatment switching. The company explained there were insufficient data to estimate the multiple parameters needed for the RPSFTM and IPE methods. It also stated that the IPCW method provided counterintuitive and clinically implausible results, and that the 2-stage method was not viable because of insufficient data and the need for a 'secondary baseline' before switching. The committee questioned whether it was necessary to adjust the results because of the likely minimal effect of multiple lines of newer treatments (see section 3.13~~3~~.13~~3~~.10~~)~~). But it appreciated the company's attempt to explore this issue, and recognised that the modified RPSFTM appeared to be a reasonable first attempt to explore this uncertainty. However, it noted that the method used was less of a 'modified' RPSFTM, and more of a 2-stage method using aspects of all adjustment approaches, and propensity weighting. It also considered that the IPCW and 2-stage methods could have been appropriate, if appropriately specified. Given the concerns around how the company adjusted for treatment switching, the committee considered that using the IPCW or 2-stage

method might have been preferred. Whether or not the measures of effectiveness were adjusted, the committee appreciated that the costs of treatments not offered in the NHS would need removing from the economic analyses. The committee concluded that it would like to see:

- other methods explored in more detail or
- the uncertainties of the modified RPSFTM approach addressed, such as the costs of treatments not offered in the NHS and unadjusted PFS2 in the COU-AA-302 trial (see section 3.9).

Using the COU-AA-302 data to estimate the effect of a second newer androgen receptor inhibitor and adjust for survival causes uncertainty

3.9 Janssen manufactures abiraterone as well as apalutamide, so has access to individual patient data from trials of abiraterone in hormone-relapsed metastatic disease. To generate the modified RPSFTM, the company used data from another trial, COU-AA-302, to estimate and adjust for the survival benefit of a second newer androgen receptor inhibitor in SPARTAN. COU-AA-302 was a randomised trial later in the treatment pathway. It compared abiraterone plus prednisone with placebo plus prednisone in people with hormone-relapsed metastatic prostate cancer who had not had cytotoxic chemotherapy. The ERG explained it could not verify the results of the modified RPSFTM because the company had not provided the requested individual patient data. Although the ERG agreed with using the COU-AA-302 data and the SPARTAN data, it noted that the survival benefit of abiraterone may be underestimated. This was because people having placebo in the trial could cross over to have abiraterone at unblinding. To address the ERG's concern, the company estimated the survival benefits of abiraterone based on the COU-AA-302 trial's interim and final analysis data. Results showed that the final analysis data cut may be affected by crossover. But the effect should be minimal for the interim data cut because only 3 people (0.55% of the 542 originally randomised to the prednisone alone arm) had crossed over at this stage. The ERG considered that using the COU-AA-302 interim or final analysis

data had only a minimal effect on the adjusted hazard ratios for overall survival. It noted that the treatment in COU-AA-302 had a considerably bigger effect on PFS2 than on overall survival. Therefore adjusting for PFS2 crossover in COU-AA-302 would have a more pronounced effect on the adjusted hazard ratios and would likely increase the cost-effectiveness estimates. The committee concluded that using the COU-AA-302 data to estimate the effect of a second newer androgen receptor inhibitor and adjust for survival benefit caused uncertainty.

It may be unnecessary to adjust survival benefit for taking more than 1 newer androgen receptor inhibitor

3.10 The committee noted that COU-AA-302 included only people who had not had a newer androgen receptor inhibitor. So, using these data would 'over adjust' for overall survival of people having a second newer androgen receptor inhibitor in SPARTAN. This was because having a second newer androgen receptor inhibitor is unlikely to be as effective as having a first newer androgen receptor inhibitor. Given that more people in the apalutamide arm of SPARTAN had a second newer androgen receptor inhibitor, adjusting for a second newer androgen receptor inhibitor in this way could bias against apalutamide. The committee agreed that using COU-AA-302 data to estimate and adjust for the survival benefit of a second newer androgen receptor inhibitor caused uncertainty (see section 3.9). It noted that using an appropriately specified IPCW or 2-stage adjustment method applied only to SPARTAN may have avoided the potential bias associated with estimating the effect of a second newer androgen receptor inhibitor based on the COU-AA-302 trial. Also, the committee understood that the newer androgen receptor inhibitors could be used only once in the prostate cancer treatment pathway (see section 3.1). Because they are likely to lack effectiveness if they have already been used, it may be unnecessary to adjust the SPARTAN survival estimates for this type of treatment switching. The committee recalled the possibility of adverse events from multiple lines of newer androgen receptor inhibitors (see section 3.8). It agreed that it could be

reasonable to consider a scenario in which people who had a second newer androgen receptor inhibitor would have had improved survival than if they had followed NHS treatment pathways. The committee concluded that it may be unnecessary to adjust for the survival benefit of a second newer androgen receptor inhibitor. But given the uncertainty, it would have liked to have seen the cost-effectiveness estimates:

- with and without adjustment for the survival benefit of a second newer androgen receptor inhibitor
- with adjustment for the costs of treatment not offered in the NHS (see section 3.8).

How the company adjusts for crossover from placebo plus ADT to apalutamide plus ADT in SPARTAN may bias results

3.11 The committee considered whether the adjusted or the unadjusted hazard ratios were more appropriate for decision making. Adjusting for crossover from the placebo plus ADT arm to the apalutamide plus ADT arm meant that the company assumed that these people had no treatment after placebo plus ADT. But, in clinical practice, people would likely be offered a novel therapy including abiraterone plus ADT or enzalutamide plus ADT as their first subsequent treatment. However, the committee was aware that people can now have darolutamide plus ADT in the NHS. The committee considered that this part of the company's analysis could have biased against placebo plus ADT. It considered that an analysis that did not adjust survival estimates for crossover could be reasonable, if it is assumed that apalutamide has similar effectiveness to abiraterone, darolutamide and enzalutamide. In such a scenario, people who crossed over from the placebo plus ADT arm to the apalutamide plus ADT arm would be assumed instead to have abiraterone, enzalutamide, or darolutamide, and would incur the costs of these. The committee agreed that the company should explore this. The committee concluded that how the company adjusted for crossover from placebo plus ADT to apalutamide plus ADT in SPARTAN may bias results.

Adjusted and unadjusted hazard ratios for overall survival and PFS2 from SPARTAN should be taken into account

3.12 For hormone-relapsed non-metastatic disease, the company explained that the adjusted (0.77, 95% CI 0.64 to 0.94) and unadjusted hazard ratios (0.78, 95% CI 0.64 to 0.96) using the modified RPSFTM for overall survival were similar. The adjusted and unadjusted results for PFS2 were also similar. The committee questioned the face validity of the results, given that adjusting made almost no difference. It considered that this might be because the company had adjusted both arms of SPARTAN. The company explained that it considered the newer androgen receptor inhibitors the bigger driver of the adjustment results because the benefit of multiple lines of these treatments is so small. In their base cases, the company and the ERG used the adjusted hazard ratios for overall survival and PFS2 for treatment switching. The committee concluded that, although the difference was minor, it would take both adjusted and unadjusted hazard ratios for overall survival and PFS2 into account in its decision making. It also concluded that the results of the adjustment analyses may be biased (see sections 3.9 and 3.10).

SPARTAN is generalisable to NHS practice for people with hormone-relapsed non-metastatic disease

3.13 The ERG considered that people in SPARTAN reflected people in UK clinical practice with hormone-relapsed non-metastatic disease. People in SPARTAN could have multiple newer androgen receptor inhibitors, which they cannot have in the NHS (see section 3.63.63.1) because they are unlikely to be as effective as having a first newer androgen receptor inhibitor (see section 3.10). Although the impact on clinical effectiveness was likely to be minimal, the committee noted that people might have adverse events (see section 3.8). Also, people might miss out on the clinical benefit of other treatments that they could have had instead of additional lines of subsequent newer androgen receptor inhibitors. So, the committee was not clear on the effect of taking multiple newer androgen

receptor inhibitors on the direction of bias. However, the committee noted that SPARTAN was a large high-quality trial measuring relevant outcomes. It concluded that SPARTAN was generalisable to NHS practice for people with hormone-relapsed non-metastatic disease.

Clinical evidence for hormone-sensitive metastatic disease

The TITAN results are in line with planned analyses

3.14 TITAN was a phase 3, randomised, multicentre trial comparing apalutamide plus ADT (n=525) with placebo plus ADT (n=527) for hormone-sensitive metastatic prostate cancer. The committee considered that people in TITAN reflected people in UK clinical practice reasonably well. TITAN's co-primary endpoints were overall survival and radiographic progression-free survival, that is, the time from randomisation to confirmed evidence of radiographic progressive disease or death from any cause. Secondary outcomes included time to cytotoxic chemotherapy. Exploratory outcomes included progression-free survival on first subsequent treatment (PFS2; see section 3.63.63.6) and health-related quality of life. The committee was aware that although these were exploratory endpoints, the company used PFS2 and EQ-5D in its cost effectiveness modelling. Health-related quality of life was measured using the EQ-5D-5 level questionnaire, the FACT-P, the Brief Pain Inventory (BPI) and the Brief Pain Inventory Short Form (BPI-SF). The final analysis for radiographic progression-free survival and interim analyses for overall survival and PFS2 were done in November 2018. At this time, most people's cancer had progressed, and the radiographic progression-free survival endpoint had been met. In November 2018, the trial was unblinded and people who had placebo could cross over to have apalutamide if their cancer had not progressed. The final analyses of overall survival and PFS2 were done in September 2020. After disease progression, people could have abiraterone and enzalutamide as subsequent treatment options. The committee concluded that the results were in line with the trial's planned analyses.

In TITAN, apalutamide plus ADT is clinically effective compared with placebo plus ADT

3.15 In TITAN:

- median radiographic progression-free survival on apalutamide plus ADT was not reached and on placebo plus ADT it was 22.1 months (HR 0.5, 95% CI 0.4 to 0.6)
- median overall survival on apalutamide plus ADT and on placebo plus ADT is academic-in-confidence and cannot be reported here
- median PFS2 on apalutamide plus ADT and on placebo plus ADT is academic in confidence and cannot be reported here.
- mean change in EQ-5D-5L visual analogue score showed no statistically significant differences between the apalutamide plus ADT and placebo plus ADT treatment arms for all treatment cycles. For example, mean change at cycle 21 on apalutamide plus ADT was 2.50 and on placebo plus ADT it was 2.04, with a difference of -0.46 (p=0.7678).

The company used the hazard ratio for the whole population (that is, people with hormone-sensitive metastatic prostate cancer) to show the effectiveness of apalutamide plus ADT for people who are not well enough to have docetaxel or who cannot tolerate it, or who choose not to have it. The committee understood that no evidence was available for this subgroup, and it considered whether any other subgroups could be used as a proxy. For example, the patient expert had explained that this subgroup is often older. The company confirmed that it did have a hazard ratio for a subgroup of older people for the endpoint of time to progression or death. But it explained that it did not use this because there were no statistically significant differences in the age interaction. The committee agreed that there would be a number of uncertainties in using age as a proxy, including confounding factors plus the usual problems of subgroup analysis with such small sample sizes. The

committee also appreciated that there were younger people who cannot or should not have docetaxel. It concluded that apalutamide plus ADT extended radiographic progression-free survival, overall survival and PFS2 when compared with placebo plus ADT and was clinically effective. However, there was no evidence available for a subgroup who cannot have docetaxel (see section 3.40).

Adjusted and unadjusted hazard ratios for overall survival and PFS2 from TITAN should be taken into account

3.16 The company adjusted for treatment switching in TITAN (as in SPARTAN, see section 3.83.83.8). In TITAN, a higher percentage of people randomised to placebo plus ADT than in SPARTAN crossed over to apalutamide plus ADT. The percentage is academic-in-confidence and cannot be reported here. The company explained that most crossover occurred between the interim and final data cuts (see section 3.143.143.14). The committee noted that the percentage was high. This meant that adjusting for crossover would likely influence the size of the reported relative efficacy effect between apalutamide plus ADT and placebo plus ADT. In its base case the company selected the unadjusted hazard ratios for overall survival and PFS2, which it considered the most conservative approach. The ERG considered it was more appropriate to adjust the hazard ratios for overall survival and PFS2. The committee was aware that, in clinical practice, people who had not had placebo plus ADT would not be offered abiraterone or enzalutamide, and agreed that both adjusted and unadjusted analyses should be considered (see section 3.113.113.10). The committee concluded that it would take both adjusted and unadjusted hazard ratios for overall survival and PFS2 into account in its decision making.

Other methods to adjust for treatment switching should be explored and uncertainties with the modified RPSFTM addressed

3.17 For people with hormone-sensitive metastatic disease, the company used the modified RPSFTM to adjust for treatment switching (as with

Issue date: May 2021

SPARTAN, see section 3.8). Treatment switching included crossing over to apalutamide and taking treatments that might alter life expectancy after progressing on either apalutamide plus ADT or ADT alone, which do not reflect NHS practice. The committee considered that the uncertainties were the same as with SPARTAN (see sections 3.8 and 3.9). It concluded that it would like to see other methods explored in more detail or the uncertainties of the modified RPSFTM approach addressed. For example, the costs of treatment not offered in the NHS and the unadjusted PFS2 results in COU-AA-302 (see section 3.9).

The company's indirect treatment comparison shows apalutamide plus ADT offers an advantage over docetaxel plus ADT for efficacy and is well tolerated

3.18 TITAN did not compare apalutamide plus ADT with docetaxel plus ADT. So the company did an indirect treatment comparison of apalutamide plus ADT with docetaxel plus ADT, for outcomes including overall survival, radiographic progression-free survival, PFS2, and safety. The network meta-analysis included TITAN and 3 randomised controlled trials linking docetaxel plus ADT to apalutamide plus ADT through the common comparator of placebo plus ADT (CHAARTED, GETUG-AFU15, STAMPEDE). The ERG was broadly satisfied with the company's approach. The results showed that apalutamide plus ADT offers a survival advantage over placebo plus ADT and over docetaxel plus ADT. The committee noted that although the hazard ratio was below 1, which indicates a benefit, the confidence interval included the possibility of no benefit. The results are academic-in-confidence and cannot be presented here. The committee concluded that the company's indirect treatment comparison showed apalutamide plus ADT offered an advantage over docetaxel plus ADT for efficacy and is well tolerated.

TITAN is generalisable to NHS clinical practice for people with metatastatic hormone-sensitive disease

3.19 In TITAN, people could have additional lines of subsequent newer androgen receptor inhibitors. This affected the treatment effect and caused uncertainty as to what people could have had instead, in the same way as in SPARTAN (see sections 3.133.133.11 and 3.13). So, the committee was unclear on the effect of taking multiple newer androgen receptor inhibitors on the direction of bias. However, the committee noted that TITAN was a large high-quality trial measuring relevant outcomes. It concluded that TITAN was generalisable to NHS clinical practice.

Adverse effects

Adverse effects with apalutamide are tolerable

3.20 The clinical experts explained that apalutamide plus ADT is well tolerated. Rash and hypothyroidism have been reported and are manageable. Treating hypothyroidism also treats fatigue, a symptom which otherwise might not be identified and treated. The committee concluded that adverse effects with apalutamide are tolerable.

Economic model

The model structure is appropriate for decision making

3.21 The company used the same model structure for hormone-relapsed non-metastatic prostate cancer and for hormone-sensitive metastatic prostate cancer. To estimate the cost effectiveness of apalutamide plus ADT compared with placebo plus ADT, the company used a partitioned survival model with health states for progression-free survival, progressed disease and death. After disease progression, people can go on to have up to 3 lines of subsequent therapy and have declining health-related quality of life. The company used PFS2 to inform the probability of moving between the first and second treatments for metastatic disease. It used mean health state durations to assign people to the remaining health states.

Within the progression-free survival health state, people could be on or off treatment as determined by trial data on time-to-treatment discontinuation. Efficacy data were informed by SPARTAN (metastases-free survival and overall survival) and TITAN (radiographic progression-free survival and overall survival). The committee concluded that the model structure was appropriate for decision making.

Modelling the SPARTAN and TITAN data

In SPARTAN, extrapolating metastases-free survival using a Weibull model is uncertain; a more flexible model is needed

3.22 Since the decision problem had a lifetime time horizon (32 years), the company sought data to estimate what would have happened had the SPARTAN trial lasted longer. The company did not identify any other studies that provided longer-term data for metastases-free survival to inform the extrapolations beyond the duration of SPARTAN. It therefore explored a range of curves to extrapolate metastases-free survival trial data from SPARTAN, including generalised gamma and Weibull. Most curves modelling metastases-free survival provided a good fit to the observed data, but the committee recognised that the observed data were limited. The company asked for clinical feedback, which suggested that the Weibull model was the most plausible for both apalutamide plus ADT and placebo plus ADT, although it could underestimate metastases-free survival at 10 years for apalutamide plus ADT. The clinical expert estimated that only 1% to 2% of people having placebo plus ADT would be metastases-free at 5 to 10 years. Therefore the Weibull model was a good fit to the observed data. In its base case, the company used the Weibull model to extrapolate metastases-free survival, and fitted the curves independently. The ERG also chose the Weibull to model metastases-free survival. However, clinical expert advice to the ERG suggested that none of the models adequately captured metastases-free survival. This was because most underestimated the proportion who remain metastases free on placebo plus ADT at 5 and 10 years. The

exception was the generalised gamma model, which had a clinically implausible long tail to the curve, and which may overestimate the proportion who remain metastases free on apalutamide plus ADT. The ERG explained that the model used had a large impact on the cost-effectiveness results. It suggested that more flexible models may be more appropriate. The committee was aware that metastases-free survival was not adjusted for treatment switching because this endpoint was reached before people could cross over between arms (see section 3.63.63.6). The committee concluded that, because of the uncertainty associated with the Weibull model, it would have liked to see a more flexible model fitted to extrapolate metastases-free survival beyond the trial duration.

In SPARTAN, extrapolating overall survival using a generalised gamma model is appropriate, but the treatment effect beyond the trial is uncertain

3.23 The company used a systematic review by Aly et al. (2018) to identify external clinical trial data that could inform survival projections for SPARTAN. It found 3 clinical trials with a similar population to SPARTAN. It referred to this as 'historical' data. But, it did not use this data to extrapolate overall survival because SPARTAN had longer follow up than the historical data studies. The company assessed if the proportional hazards assumption held for overall survival. The log-cumulative hazard plot for overall survival in both arms of SPARTAN showed that the curves were relatively parallel over time. The company stated that based on a statistical test (the Schoenfeld test), the proportional hazards assumption seemed to hold, because the resulting p-value was not significant (p=0.7321). Therefore, in its original base case, the company considered it appropriate to apply jointly fitted models. That is, rather than fitting survival models to each treatment independently, the company fitted 1 survival model to all data, and then generated treatment-specific survival curves by using the treatment group as a covariate. The company chose a Weibull distribution for extrapolating overall survival because of

its clinical plausibility. However, the ERG could not verify that proportional hazards would hold in the extrapolated part of the survival curves because of lack of evidence. It noted that the survival estimates from SPARTAN, on which the proportional hazards assumption was tested, were immature. Therefore, it considered that using models fitted to the treatment arms separately (independently) would be more appropriate. During technical engagement before the committee meeting, expert advice to the ERG was that both Weibull curves were likely to underestimate overall survival at 10 years, and possibly at 15 years. The ERG further noted that generalised gamma models have a good visual fit to the observed data, and better statistical fits (lower Akaike information criterion [AIC]/Bayesian information criterion [BIC] scores) compared with the Weibull models. After technical engagement, the company followed the expert's advice and, in their base cases, both the company and the ERG used the jointly fitted generalised gamma models. The committee was aware that the company had adjusted overall survival for treatment switching because of people who died; many did so after unblinding and the final analysis of SPARTAN (see section 3.63.63.6). The committee concluded that extrapolating overall survival using the generalised gamma model seemed appropriate, but the treatment effect beyond the observed trial period was uncertain.

In SPARTAN, extrapolating PFS2 using a Weibull model is appropriate, but estimates are based on immature data

3.24 The company, having assessed that the proportional hazards assumption held for PFS2, applied the Weibull models fitted jointly to both arms in its base case. This was based on the statistical fits (AIC/BIC scores) and clinical plausibility. The ERG also jointly fitted Weibull models in its base case, although it noted that the estimates were likely uncertain because data for PFS2 for apalutamide plus ADT in SPARTAN was relatively immature. The committee concluded that the company and ERG's approach to modelling PFS2 was broadly appropriate, but agreed that it was based on immature data.

In TITAN, extrapolating radiographic progression-free survival using a Weibull model is uncertain; a more flexible model is needed

3.25 The company assessed whether the proportional hazards assumption held for radiographic progression-free survival. Based on the log-cumulative hazard plot for radiographic progression-free survival, and a statistical test (the Schoenfeld test), it considered that the proportional hazards assumption may be violated. The company therefore decided to fit parametric curves to both arms independently. Based on clinical advice, it chose Weibull curves for its base case. The ERG also chose Weibull curves for its base case for both treatments. But it noted that radiographic progression-free survival data for apalutamide plus ADT was highly immature, which is a large driver of the cost-effectiveness results. The ERG also noted that the Weibull models have worse statistical fit (that is, higher AIC and BIC scores) than other models. The committee appreciated these measures reflected the model fit, but only to the observed data. Also, expert advice to the ERG suggested that the Weibull models are likely to underestimate the proportion of people who progressed in the ADT arm at 5, 10 and possibly 15 years. Therefore, the ERG suggested that more flexible models may be more appropriate. The committee concluded that, because of the uncertainty with the Weibull model, it would have liked to have seen a more flexible model fitted to extrapolate radiographic progression-free survival beyond the duration of TITAN.

The TITAN post-progression survival results lack face validity; a more flexible model for extrapolating overall survival is needed

3.26 The company collected historical data for ADT because overall survival estimates from TITAN were immature. The upper boundary of the confidence interval for median overall survival was not estimable because not enough events had occurred. The company did a systematic literature review and found 7 published trials with ADT arms which had longer follow up than TITAN. It pooled survival data for the ADT arms of these

studies and follow-up duration reached about 9 years. The ERG considered this a good attempt to collect longer follow-up data although it noted that only studies published after 2013 were included. The ERG could not verify the company's work because the company did not share its systematic review. The company assumed a common shape between the ADT arm, reflecting pooled data, and the placebo plus ADT arm in TITAN. Based on expert opinion, it chose the Weibull curves in its base case because these provided the most clinically plausible extrapolations. Expert advice to the ERG was that survival at 5, 10 and possibly 15 years in both treatment arms was higher in practice than estimated by the Weibull models. Despite this, the ERG chose the Weibull model for its base case because it gave the most conservative estimates. It suggested that more flexible models may be more appropriate. The committee was aware that people have a treatment until disease progression. It noted that the company's model showed that people with hormone-sensitive metastatic disease had longer post-disease progression survival if they had apalutamide plus ADT than either docetaxel or ADT plus placebo. Yet the committee was aware that people had fewer post-progression treatment options when they started apalutamide. The post-progression estimates are academic-in-confidence and cannot be reported here. The committee considered that this lacked face validity and biological plausibility. It concluded that, because of the uncertainty with the Weibull model, it would have liked to have seen a more flexible model fitted to extrapolate overall survival beyond the trial duration. The committee further concluded that it would like to see evidence justifying the difference in post-progression survival between treatment arms as well as scenarios exploring equal post-progression survival between apalutamide plus ADT and its comparators.

In TITAN, extrapolating PFS2 is uncertain because it is based on immature data

3.27 The company, having assessed that the proportional hazards assumption held for PFS2, applied a Weibull model fitted jointly to both arms in its

base case. This was based on clinical plausibility and consistency (which helps to avoid the issue of curves crossing) with the curves for radiographic progression-free survival (see section 3.25) and overall survival (see section 3.26). The ERG noted that both the Weibull and Gompertz models have the best statistical fits to the observed data. However, the Weibull model is likely to overestimate PFS2 at 10 and 15 years for the apalutamide plus ADT arm. Also, people seem to spend almost no time on the third-line treatment for metastatic disease. Therefore, the ERG considered that the Gompertz model was the only clinically relevant alternative although it is also likely to overestimate long-term survival in the apalutamide plus ADT arm. The ERG noted that, because the PFS2 estimates were immature in TITAN, extrapolating PFS2 assuming proportional hazards was likely to be highly uncertain. For radiographic progression-free survival and overall survival, the ERG suggested that more flexible approaches would be appropriate. The committee concluded that the true estimates of PFS2 after the end of the trial were uncertain because these were based on immature data.

Treatment effect waning has little effect on the cost-effectiveness results

3.28 The company considered that the relative benefits of apalutamide did not wane over time so did not apply any treatment effect waning in its base cases. It justified this, noting there was no evidence in SPARTAN or TITAN that the overall survival curves for both treatments converge over time. The ERG explored treatment effect waning but was unclear from the hazard plots if treatment benefit declined. Because no waning effect had been seen in clinical trials for another prostate cancer drug (abiraterone) with a longer follow up, the experts to the ERG did not expect to see treatment effect waning with apalutamide. However, a study in advanced prostate cancer (Antonarakis et al. 2016) suggested that resistance to newer androgen receptor inhibitors, such as enzalutamide and abiraterone, was likely to develop with time. The ERG noted that it was unclear if the study results were generalisable to hormone-relapsed non-metastatic disease. The ERG also noted that resistance to abiraterone or

enzalutamide does not necessarily imply that there would be a treatment waning effect. It considered that there was insufficient evidence to assess the best approach for duration of treatment benefits. The Cancer Drugs Fund clinical lead noted that, in clinical practice, most newer drugs for prostate cancer seem to lose at least some of their effectiveness over time. The committee was aware that both the company and the ERG had explored treatment waning in their original scenarios (that is, before technical engagement). The effect on the incremental cost-effectiveness ratio (ICER) was an increase of around £2,000 per quality-adjusted life year (QALY) gained when varying treatment effect waning from 100% to 0% for a duration of 5 years and 10 years. The committee concluded that treatment effect waning seemed to have a small impact on the cost-effectiveness results.

Treatment costs

The cost of apalutamide may be underestimated in the model

3.29 The committee was aware that apalutamide was being offered at a discount. It was also aware that duration of treatment determines cost. People would have apalutamide plus ADT until disease progression, or until they can no longer tolerate them or choose to stop taking them. The company explained that time-to-treatment discontinuation reflected the SPARTAN data cut of February 2020. Instead it chose to model time on treatment using metastases-free survival, calculated at an earlier data cut in May 2017. The company explained this was because several of the extrapolations for time-to-treatment discontinuation crossed the metastases-free survival curves towards the end of SPARTAN. The company and committee did not consider this would reflect practice because it contradicted apalutamide's summary of product characteristics, which states that people would stop treatment after progressing. Similarly, for TITAN the company said that it took time-to-treatment discontinuation and radiographic progression-free survival from TITAN data cuts that occurred at different times. The company explained that the costs used in

the model were informed by the minimum of either time-to-treatment discontinuation until progression, or metastasesfree survival curves. The company therefore capped the costs, which it noted might have slightly underestimated the cost of apalutamide in the model. The committee concluded that cost of apalutamide might have been underestimated in the model, and it would take this into account in its decision making.

Utility values

The ERG's utility values, unadjusted for line of treatment and difference in population, are appropriate

3.30 The company assumed that health-related quality of life declines over time as people in the model develop metastatic disease and move onto subsequent lines of therapy (see section 3.213.213.19). The utility value used for taking the first treatment for hormone-relapsed metastatic prostate cancer was from SPARTAN using the EQ-5D-3L. The utility values are considered confidential by the company so cannot be reported here. For second and third treatments for hormone-relapsed metastatic prostate cancer, the company used external data from NICE's technology appraisal guidance on abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA387). This was because a limited number of people completed the EQ-5D-3L questionnaire after developing metastases in SPARTAN. The company derived the utility values for second and third treatments from the first treatment by applying a 'relative decline ratio'. This was estimated by dividing the TA387 utility value for second-line treatment of hormone-relapsed metastatic disease by the TA387 utility value for first-line treatment of hormone-relapsed metastatic disease. This value was then multiplied by the utility value for the first hormone-relapsed metastatic disease treatment in the company's trials. This process was repeated to estimate the utility value for the third treatment for hormone-relapsed metastatic disease. The company adjusted the derived utility values to account for population differences between SPARTAN and TA387. This

was in line with the method described in the NICE Decision Support Unit's technical support document 12 on the use of health state utility values in decision models. The ERG had concerns with the company's adjusted utility values:

- They were much lower than those used in NICE's technology appraisal guidance on enzalutamide for treating metastatic hormone-refractory prostate cancer before chemotherapy is indicated (TA377) and enzalutamide for hormone-relapsed non-metastatic prostate cancer (TA580). The utility values were 0.658 and 0.612 in TA377 and 0.8 and 0.688 in TA580, for health states reflecting second- and third-line treatments of hormone-relapsed metastatic prostate cancer.
- It was unclear which line of treatment generated the utility values reported in TA387.
- By applying a 'relative decline ratio', the company assumed that the utility values would decrease by the same relative proportion between first-line and second-line treatments of hormone-relapsed metastatic prostate cancer (as in TA387). But, the committee considered that this assumption may not be appropriate given the different starting populations in this appraisal (hormone-relapsed non-metastatic disease or hormone-sensitive metastatic disease) and in TA387 (hormone-relapsed metastatic disease before chemotherapy is indicated).

In its base case, the ERG used the utility values from TA377 without adjusting them. The company used the same approach to derive utility values for second-line and third-line treatments of hormone-relapsed metastatic prostate cancer. The utility values are considered confidential by the company so cannot be reported here. The patient experts reiterated the effect of psychological distress (see section 3.33.33.3) and worry about a treatment's loss of efficacy. The clinical expert was aware that EQ-5D, measured in SPARTAN, included questions on anxiety and depression and agreed with the company's utility values. The committee agreed that this disease was

Issue date: May 2021

associated with a significant impact on quality of life. However, it was concerned with the lack of consistency with the utility values used in related technology appraisals. Also, the Cancer Drugs Fund clinical lead explained that the ERG's unadjusted utility values better fitted what had been seen in other disease areas with multiple lines of treatment. The committee therefore agreed that, on balance, the ERG's utility values had a higher face validity than the company's adjusted utility values. It concluded that the ERG's unadjusted utility values were most appropriate for decision making.

Modelling the adverse effects of docetaxel

The company and ERG's cost estimates are satisfactory

3.31 In the original model, the company assumed that the adverse effects of docetaxel occurred throughout the entire hormone-sensitive metastatic prostate cancer pre-progression health state. At technical engagement before the committee meeting, the ERG explained that this overestimated the costs of managing adverse effects, and it was more appropriate to apply those costs for the first 6 months. The company agreed that this overestimated the costs but suggested that after 6 months of treatment there would be additional costs associated with the adverse effects of ongoing ADT. Therefore, in its base case, the company applied the costs of managing adverse effects for docetaxel for 6 months and the costs of managing adverse effects for ADT alone thereafter. The ERG's base case reflected the company's assumption. The clinical experts explained that the adverse effects associated with docetaxel were likely to last for 6 to 12 months. The committee concluded that the company and ERG's cost estimates were satisfactory.

The committee is satisfied with the ERG's incidence rates for neutropenia and febrile neutropenia

3.32 The company's model included grade 3 to 4 neutropenia and febrile neutropenia, which are adverse effects associated with docetaxel. The

rates of these in the hormone-sensitive metastatic pre-progression phase were based on a real-world study on the use of docetaxel in the NHS (Patrikidou et al. 2017). These were 36.3% for neutropenia and 18.2% for febrile neutropenia per course of 6 cycles of docetaxel. The company suggested that these rates may be low compared with observational data. The ERG noted that the company's sources of observational data had methodological limitations including no information on patient numbers. In its base case the ERG used pooled data from 3 docetaxel trials (GETUG-AFU15, STAMPEDE and CHAARTED). It estimated combined rates of 10.6% for febrile neutropenia and 15.4% for neutropenia, at a constant rate over 6 months. STAMPEDE included only people from the UK and Switzerland, and therefore was more likely to represent NHS clinical practice. The committee concluded that it was satisfied with the ERG's pooled incidence rates for neutropenia and febrile neutropenia.

End of life

The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. The company did not make a case for end of life in its submission. The committee noted that the life expectancy of people who had ADT alone would normally be longer than 24 months.

The end of life criteria are not met for apalutamide in hormone-relapsed non-metastatic prostate cancer

3.33 In SPARTAN the median overall survival was 59.9 months (for placebo plus ADT) and the median improvement in life expectancy was 14 months. The committee concluded that the end of life criteria were not met for apalutamide in hormone-relapsed non-metastatic prostate cancer.

The end of life criteria are not met for apalutamide in hormone-sensitive metastatic prostate cancer

3.34 In TITAN the median overall survival for placebo plus ADT was not reached; the mean overall survival estimated in the company's base case

Issue date: May 2021

was 4.6 years. The committee noted that the mean improvement in life expectancy was 6 months (compared with docetaxel plus ADT) and 17 months (compared with placebo plus ADT) in TITAN. It concluded that the end of life criteria were not met for apalutamide in hormone-resistant non-metastatic prostate cancer.

Cost-effectiveness estimates for apalutamide for hormone-relapsed non-metastatic disease

An acceptable ICER would be in the middle of the range normally considered cost effective

3.35 NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee was aware that the unmet need had lessened because NICE has recommended darolutamide. The data are immature for overall survival and PFS2 and the appropriate extrapolation model for metastases-free survival was uncertain. So the committee agreed that an acceptable ICER would be in the middle of the range normally considered a cost-effective use of NHS resources (that is, £20,000 to £30,000 per QALY gained).

Apalutamide is not cost effective for hormone-relapsed non-metastatic disease

3.36 Because of confidential commercial arrangements for apalutamide and other treatments in the pathway, the cost-effectiveness estimates cannot be reported here. The committee noted that the ERG's analyses better reflected the committee's preferred assumptions. These included:

- adjusting for treatment switching for overall survival and PFS2 (see section 3.113.113.10)
- using unadjusted utility values for second-line and third-line hormone-relapsed metastatic prostate cancer (see section 3.303.303.30).

- To offset uncertainty, the company increased its discount for apalutamide. Because the discount is confidential, the new ICERs were discussed at a private second committee meeting. The committee reviewed the deterministic ICERs and noted that these did not include its preferred assumptions, and it was not presented with the probabilistic ICERs or with analyses that reflected the uncertainty. It considered that the ICER that most closely reflected its preferred assumptions is higher than what would be considered a cost-effective use of NHS resources. Also, if its preferred assumptions were included, it would likely increase the ICER. Therefore, apalutamide could not be recommended as a cost-effective use of NHS resources for treating hormone-relapsed non-metastatic prostate cancer.

For hormone-relapsed non-metastatic disease the uncertainties should be explored

3.37 The ERG's base case best reflected the committee's preferred assumptions, but several uncertainties should be explored, including:

- other adjustment methods and analyses for treatment switching, such as IPCW or 2-stage methods, or addressing the uncertainties of the modified RPSFTM approach (see section 3.8)
- cost-effectiveness estimates with and without adjustment for survival benefit of a second newer androgen receptor inhibitor, with the removal of the costs of treatments not offered in the NHS (see sections 3.8 and 3.10), but accounting for the fact that people who crossed over from placebo plus ADT to apalutamide plus ADT may have instead had abiraterone, enzalutamide, or darolutamide
- justification of the difference in post-progression survival between treatments and scenarios including equal post-progression survival between apalutamide plus ADT and its comparators (see section 3.26)

- a more flexible method to extrapolate metastases-free survival (see section 3.223.223.22).

Cost-effectiveness estimates for apalutamide for hormone-sensitive metastatic disease

An acceptable ICER would be below the middle of the range normally considered cost effective

3.38 The data are immature for overall survival and PFS2 and there was uncertainty about the appropriate extrapolation model for radiographic progression-free survival, overall survival and PFS2. So the committee agreed that an acceptable ICER would be below the middle of the range normally considered a cost-effective use of NHS resources (that is, £20,000 to £30,000 per QALY gained).

Apalutamide is not cost effective for hormone-sensitive metastatic disease

3.39 Because of confidential commercial arrangements for apalutamide and subsequent treatments, the cost-effectiveness estimates cannot be reported here. The committee was satisfied with some of the ERG's preferred assumptions. These included:

- adjusting for treatment switching for overall survival and PFS2 (see section 3.16)
- using unadjusted utility values for second-line and third-line metastatic disease (see section 3.30)
- using pooled incidence rates for neutropenia (15.4%) and febrile neutropenia (10.6%; see section 3.32)
- incremental cost-effectiveness analyses including docetaxel plus ADT, apalutamide plus ADT, and ADT alone.

To offset uncertainty, the company increased its confidential discount for apalutamide after the committee's first meeting. Because the

discount is confidential, the new estimates of cost effectiveness were discussed at a private second committee meeting. Based on incremental deterministic ICERs, the committee agreed that the cost-effectiveness estimates for docetaxel plus ADT were below the range normally considered a cost-effective use of NHS resources, whereas the cost-effectiveness estimates for apalutamide plus ADT were above £30,000 per QALY gained. Therefore apalutamide could not be recommended as a cost-effective use of NHS resources for treating hormone-sensitive metastatic prostate cancer.

Apalutamide is not cost effective for hormone-sensitive metastatic disease in a subgroup of people who cannot have docetaxel

3.40 The committee went on to consider the population who cannot or should not have docetaxel. It recalled that TITAN excluded people with poor performance scores, but did include older people. The committee was aware of data from consultees and from NHS England documenting the association between older age and decreasing use of docetaxel for hormone-sensitive disease. It was also aware of subgroup analyses from TITAN which showed a hazard ratio for progression or death of 0.65 for people over 75 years compared with hazard ratios of 0.57 and 0.74 for younger age groups. The company tested all subgroups for interaction and found none. The committee recognised that data might not be available for all of the inputs to this model, but that a modelled scenario for this group should be presented nonetheless. The committee considered that it should include:

- a population with a baseline survival curve reflecting an older more unwell population
- a measure of effect that recognises uncertainty, including the possibility that apalutamide is less effective for this population than for the population in TITAN
- utility values reflecting an older more unwell population and

- a model in which people do not go on to get docetaxel or cabazitaxel when their disease becomes hormone relapsed.

  In its response discussed at the private committee meeting, the company attempted to model a group who cannot or should not have docetaxel, by:

- using a poorer baseline prognosis by proportionally reducing progression-free survival, PFS2 and overall survival (to explore worsening of baseline survival)
- using the ERG's preferred assumptions for treatment effectiveness (to explore reducing apalutamide's treatment effect)
- reducing utility values for all lines of treatment by 10% (to explore utility values reflecting the older more unwell population)
  removing subsequent chemotherapy (to explore a model in which people do not go on to get docetaxel or cabazitaxel when their disease becomes hormone relapsed).

  The committee appreciated the company's attempt to explore this issue. But it remained concerned that the effectiveness of apalutamide for the older and more unwell population was the same as for the younger and less unwell population. The committee considered that because it had not been presented with any evidence, it was unsure whether apalutamide was equally effective in both populations. Also, it considered that it would be unlikely to make age-based recommendations. The committee wished to see analyses that took into account this uncertainty. It agreed that the probabilistic ICERs were more likely than the deterministic ICERs to capture the uncertainty associated with these analyses, and were likely to be higher. However, the company had not presented these. Also, the company had not fully implemented the committee's preferred assumptions outlined in section 3.383.383.39, which was a further source of uncertainty. The company did not present evidence or analyses for people with low-

volume and low-risk disease, who the company noted were less likely to have docetaxel plus ADT (see section 3.5). The committee considered that the ICER that most closely reflected its preferred assumptions is above what it would consider a cost-effective use of NHS resources. Also, if its preferred assumptions were included and the uncertainties outlined above taken into account, it would likely increase the ICER. Taking all this into account, apalutamide could not be recommended as a cost-effective use of NHS resources for treating hormone-sensitive metastatic prostate cancer in a subgroup of people who cannot have docetaxel.

For hormone-sensitive metastatic disease the uncertainties should be explored

3.41 The ERG's base case best reflected the committee's preferred assumptions, but several uncertainties should be explored including:

- other adjustment methods and analysis for treatment switching, such as IPCW or 2-stage methods, or addressing the uncertainties of the modified RPSFTM approach (see sections 3.8 and 3.17)
- cost-effectiveness estimates with and without adjustment for survival benefit of a second newer androgen receptor inhibitor, with the removal of the costs of treatments not offered in the NHS (see sections 3.8, 3.10 and 3.17), but accounting for the fact that people who crossed over from placebo plus ADT to apalutamide plus ADT may have instead had abiraterone, enzalutamide, or darolutamide
- justification of the difference in post-progression survival between treatments and scenarios including equal post-progression survival between apalutamide plus ADT and its comparators (see section 3.26)
- more flexible methods for extrapolating radiographic progression-free survival, overall survival and PFS2 (see sections 3.25 to 3.27).

Innovation

Apalutamide is not innovative for hormone-relapsed non-metastatic prostate cancer

3.42 Darolutamide, a new androgen receptor inhibitor that was not available when this appraisal started is now an option with ADT for treating hormone-relapsed non-metastatic prostate cancer in the NHS. The recommended dose of darolutamide is twice daily, and the recommended dose of apalutamide is once daily (as 4 tablets). The committee considered this an advantage, but concluded that this was not sufficient to consider apalutamide plus ADT a step-change in treatment and therefore innovative.

Apalutamide may be innovative for hormone-sensitive metastatic prostate cancer

3.43 The company considered apalutamide plus ADT to be innovative because it is an oral treatment, and requires less monitoring than docetaxel plus ADT. The committee agreed that apalutamide plus ADT would fulfil an unmet need, particularly for people who cannot or should not take docetaxel. The committee was aware that there are other androgen receptor inhibitors with marketing authorisations for this indication, notably enzalutamide and abiraterone, but none are currently recommended by NICE. It concluded that there was a possible case for innovation but it would depend on the outcome of ongoing apraisals.

Equality issues

The recommendations apply to all people with prostate cancer

3.44 The committee noted that, as in previous NICE technology appraisals of prostate cancer treatments, its recommendations should apply to all people with prostate cancer. It further noted that a person can have a prostate but not identify as a man. Gender reassignment is a protected characteristic under the Equality Act 2010. The committee also noted that,

in clinical practice, older people are less likely to have docetaxel than younger people. It was aware that although docetaxel is more likely to be contraindicated or unsuitable for older people, age alone will not determine whether a person could or should have docetaxel in clinical practice. The committee was also aware that making recommendations by age to reflect people who cannot or should not have docetaxel could discriminate against younger people for whom docetaxel is contraindicated or unsuitable. The committee concluded that, by considering the cost effectiveness for people who could not or should not have docetaxel (see sections 3.15 and 3.40), it took into account older people in its recommendations.

4 Review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, appraisal committee
May 2021

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Issue date: May 2021

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Aminata Thiam
Technical lead

Carl Prescot
Technical adviser

Shonagh D'Sylva
Project manager

ISBN: [to be added at publication]

Issue date: May 2021

NICE National Institute for Health and Care Excellence

Apalutamide for treating prostate cancer [ID1534]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Friday 11 June 2021 email:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Janssen-Cilag Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**
Name of commentator person completing form:	**Nicola Trevor**

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

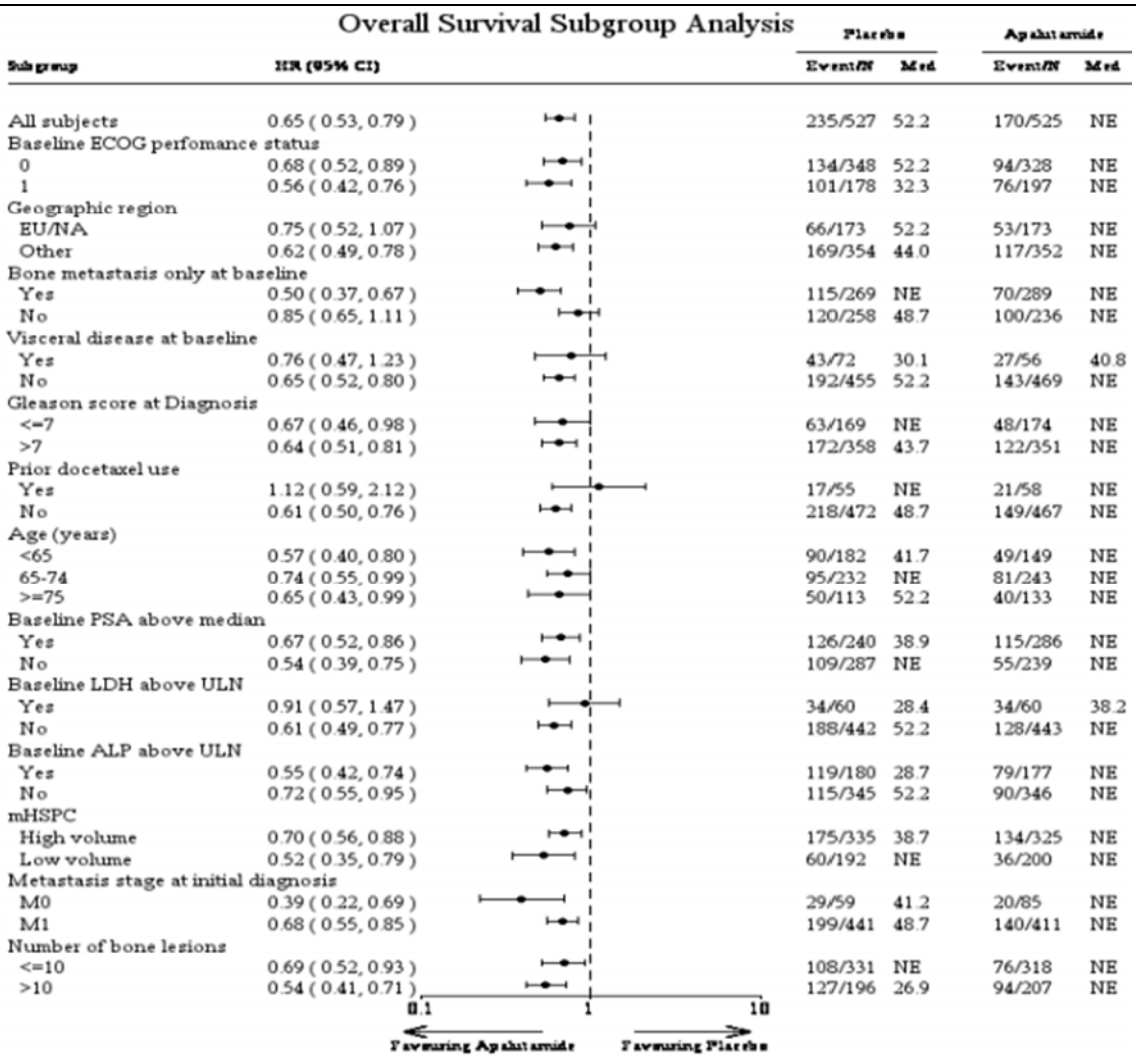
Please return to: **NICE DOCS**

Apalutamide for treating prostate cancer [ID1534]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Friday 11 June 2021 email:** NICE DOCS

Janssen welcomes the opportunity to comment on the preliminary recommendation made by the Appraisal Committee (AC) detailed in the appraisal consultation document (ACD). We are disappointed that the AC's preliminary decision is to not recommend apalutamide for patients with non-metastatic hormone relapsed prostate cancer (nmHRPC) at high risk of metastasising and metastatic hormone sensitive prostate cancer (mHSPC). We are, however, committed to working with the National Institute for Health and Care Excellence (NICE) to address the AC's key concerns, as outlined in the ACD, in order to gain access for patients and address the unmet need in both settings. As stated in Section B.1.3.1 of the company submission, high-risk nmHRPC, and mHSPC is analogous to breast cancer, where novel treatments are initiated early to prevent recurrence or progression to metastatic disease for patients at high risk of disease progression.(1) Indeed, the main goal for the treatment of patients with high-risk nmHRPC, and mHSPC, is to delay the development of mHRPC because this disease state is associated with debilitating prostate cancer symptoms, impaired health-related quality of life (HRQL), greater resource use and healthcare costs, and poorer prognosis.(2-4) Despite this similarity in aims of therapy and disease severity between early prostate cancer and early breast cancer, there is a disparity in the number of novel treatments available for patients with each condition. Recently, NICE have recommended one novel therapy for high-risk nmHRPC (darolutamide plus androgen deprivation therapy [ADT])(5) and one novel therapy for mHSPC (enzalutamide plus ADT).(6) By contrast, multiple novel treatments for early breast cancer have been recommended and are available as treatment options for patients and clinicians.(1) Apalutamide plus ADT offers a solution towards addressing this inequity. An unmet need still exists for patients with nmHRPC and mHSPC, despite the availability of darolutamide plus ADT/enzalutamide plus ADT. High risk nmHRPC and mHSPC are heterogeneous diseases and as such, an additional treatment option would allow clinicians the flexibility to select the most appropriate therapy for individual patients.(7, 8) The major European treatment guidelines recommend apalutamide plus ADT, darolutamide plus ADT or enzalutamide plus ADT as treatment options for patients with high-risk nmHRPC(9, 10) The guidelines also recommend multiple treatment options for mHSPC including ADT in combination with docetaxel, abiraterone, enzalutamide or apalutamide.(9, 11)	
1	**Population who do not currently receive docetaxel** *"The Cancer Drugs Fund clinical lead noted that in NICE's technology appraisal on abiraterone for newly diagnosed high-risk hormone-sensitive metastatic prostate cancer (in development) around two-thirds of people with hormone-sensitive metastatic prostate cancer in England have ADT alone"* [ACD: Section 3.5, p8] *"The committee recognised that there are 2 distinct populations who do not have docetaxel plus ADT…People who cannot or should not have docetaxel…People who choose not to have docetaxel"* [ACD: Section 3.5, p8/9] *"TITAN was a large high-quality trial measuring relevant outcomes. It [the committee] concluded that TITAN was generalisable to NHS clinical practice"* [ACD: Section 3.19, p21] As highlighted in the ACD, the majority (two-thirds) of mHSPC patients do not currently receive treatment with docetaxel. Janssen agree with this assertion which is also supported by data from the national prostate cancer audit, which estimates that only 27% of newly diagnosed metastatic prostate cancer patients receive docetaxel.(12) These data are also supported by clinical expert opinion, which suggests that only 30% of all mHSPC patients receive docetaxel.(13) This means between 67% and 73% of mHSPC patients are ineligible or otherwise unsuitable for chemotherapy. Janssen disagrees, however, with the committee's statement that "there are two distinct populations who do not have docetaxel plus ADT". Whilst true in a newly diagnosed, high-risk mHSPC patient population, this categorisation does not hold in an all-comers patient population. Multiple factors contribute to a patient's suitability to receive docetaxel. The main subgroups of patients who do not currently receive docetaxel and the reasons for this may be summarised as follows: • Metastasis stage at diagnosis of non-metastatic (M0) - these patients do not meet the inclusion criteria of the NHS England commissioning policy for docetaxel which requires patients to "have newly diagnosed, metastatic, prostate cancer"(14) • Low volume (LV) disease - docetaxel is not as effective in patients with low volume disease. Add-

	on docetaxel showed no survival benefit in LV disease in CHAARTED and GETUG-AFU 15 compared to ADT alone.[15-17] As such, patients with LV disease would not routinely be offered docetaxel in clinical practice • Unsuitable due to fitness/co-morbidity - unsuitable due to clinical prognostic factors: age, performance status or comorbidities. These factors are listed as exclusion criteria in the NHS England commissioning policy for docetaxel[14] With respect to generalisability of the treatment effect of apalutamide observed in TITAN to patients who are ineligible or otherwise unsuitable for chemotherapy, there are three reasons to consider that this effect is generalisable: 1. As a targeted novel hormone therapy, the mechanism of action for apalutamide is wholly distinct to that of chemotherapy. 2. The treatment effect of apalutamide plus ADT has been demonstrated consistently across all pre-specified subgroups (Figure 1). 3. Clinicians have stated that they are comfortable prescribing apalutamide to these patients, whose only treatment option is ADT alone.[13] Indeed, subgroup analyses for overall survival (OS), presented in Figure 1, show consistency with the overall study results. The hazard ratio of the subgroups for patients who do not currently receive docetaxel (age, baseline Eastern Cooperative Oncology Group (ECOG) performance status, disease volume, metastasis stage at diagnosis) are all <1, with confidence intervals (CI) that do not cross 1. Further, interaction effects were formally tested to determine if the magnitude of the treatment effect associated with adding apalutamide to ADT for OS differed within the categories of each prespecified subgroup. As shown in Table 1, there were no statistically significant differences in the treatment effect of these subgroups. The generalisability of the TITAN trial to the majority of mHSPC patients, may reasonably be considered no more challenging than the generalisability of most cancer trials, where patients recruited are generally younger and fitter than patients in UK clinical practice. **Figure 1. OS subgroup analysis in the TITAN trial (Final analysis; clinical cut-off date 7th September 2020; ITT population)**



Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EU, European Union; ITT, intention-to-treat; NA, North America; OS, overall survival; PS, performance status.
Notes: OS was defined as time from randomisation to death from any cause
Data were stratified by region (North America and European Union vs other countries), Gleason score at diagnosis (≤ 7 vs > 7) and prior docetaxel use (yes vs no).
Source: TITAN FA TLR 2020[18]

Table 1. OS Interaction effects tests for subgroups relevant for patients who are unsuitable/ineligible for docetaxel in TITAN (Final analysis; clinical cut-off date 7th September 2020; ITT population)

	<table><tr><th>Subgroup</th><th>Interaction effects test for OS p-value</th></tr><tr><td>Age</td><td>0.4841</td></tr><tr><td>Baseline ECOG</td><td>0.3948</td></tr><tr><td>Volume of disease</td><td>0.3344</td></tr><tr><td>Metastasis stage at diagnosis, M0</td><td>0.1411</td></tr></table> **Abbreviations:** ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; M0, non-metastatic; OS, overall survival To further explore the cost-effectiveness of apalutamide in patients who do not currently receive treatment with docetaxel, data from multiple relevant sub-groups within TITAN have been used to inform the extrapolated survival curves. These include: • Metastasis stage at diagnosis of M0 (non-metastatic) • Low volume disease • Unsuitable due to fitness/co-morbidity o Patients with a baseline ECOG score of 1 o Patients over the age of 75 o Patients with a baseline ECOG score of 1 who are over 75 years old Note that in TITAN, high-volume mHSPC was defined as 1) visceral metastases and at least 1 bone lesion or 2) at least 4 bone lesions, with at least 1 bone lesion outside of the vertebral column or pelvis. Low-volume mHSPC was defined as the presence of bone lesion(s) not meeting the definition of high-volume mHSPC. Given the challenges in identifying patients who are unsuitable for treatment with chemotherapy due to poor fitness or comorbidities within TITAN, three proxy sub-groups have been explored. Although none of these sub-groups accurately reflects the group of patients who are unsuitable for treatment with chemotherapy, they do provide some indication of the potential impact that increasing the average ECOG score and age of patients, has on the results of the cost-effectiveness analysis. In addition to these sub-group analyses, a scenario analysis which reduces the utility values applied in each health state is also presented to capture the impact on the results of worsening the health-related quality of life of patients who are unsuitable for chemotherapy. Finally, given that patients who are unsuitable for docetaxel at baseline may never receive chemotherapy at any point in the treatment pathway, an additional scenario is presented which assumes that no patients will receive docetaxel or cabazitaxel as subsequent treatment options. Results of these scenario analyses maintaining committee preferred assumptions for mHSPC are presented in Section 7 (clinical results are provided in Appendix A). Apalutamide plus ADT is cost-effective across the board in patients who do not currently receive docetaxel in clinical practice.
2	**Model face validity** *"The committee would like to see a justification of the difference in post-progression survival between treatments and scenarios including equal post-progression survival between apalutamide plus ADT and its comparators"* [ACD: Section 3.26, p26; Section 3.37, p34; Section 3.41, p38] The committee have expressed concerns regarding the face-validity of Janssen's economic model; particularly with respect to mHSPC. These concerns have arisen due to factual inaccuracies in the slides (slides 29 and 68) presented at the committee meeting of 4th March 2021. The slides presented, indicated

that Janssen had modelled substantial post-progression survival benefit for apalutamide plus ADT versus ADT alone and versus docetaxel plus ADT. In fact, Janssen have modelled a decrement in post-progression survival versus docetaxel plus ADT and a modest benefit versus ADT alone.

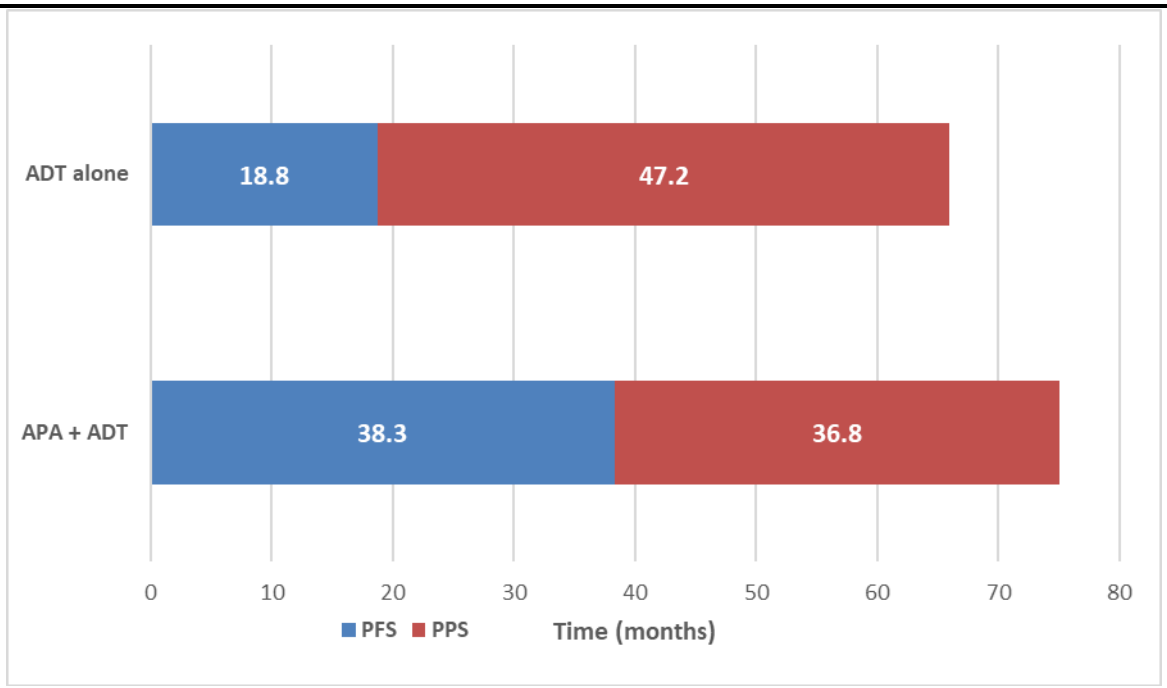
Table 2 compares the estimates in the slides, with the true mean life year estimates split by pre- and post-progression from the company's base-case analysis, while Figure 2 and Figure 3 present corrected versions of the figures presented in the committee slides.

Table 2. Pre and post progression survival estimates

	Committee slides (Mean life years: months)		Company model (Mean life years: months)	
	Pre-progression	**Post-progression**	**Pre-progression**	**Post-progression**
nmHRPC				
APA + ADT	25.5	49.5	38.3	36.8
ADT alone	9.2	56.7	18.8	47.2
Incremental	16.3	-7.2	19.5	-10.4
mHSPC				
APA + ADT	17.6	58.9	41.7	34.8
ADT alone	9.5	46.5	27.6	28.4
Docetaxel + ADT	15.7	52.6	32.5	35.9
Incremental vs ADT alone	8.1	12.4	14.1	6.4
Incremental vs docetaxel + ADT	1.9	6.3	9.2	-1.1

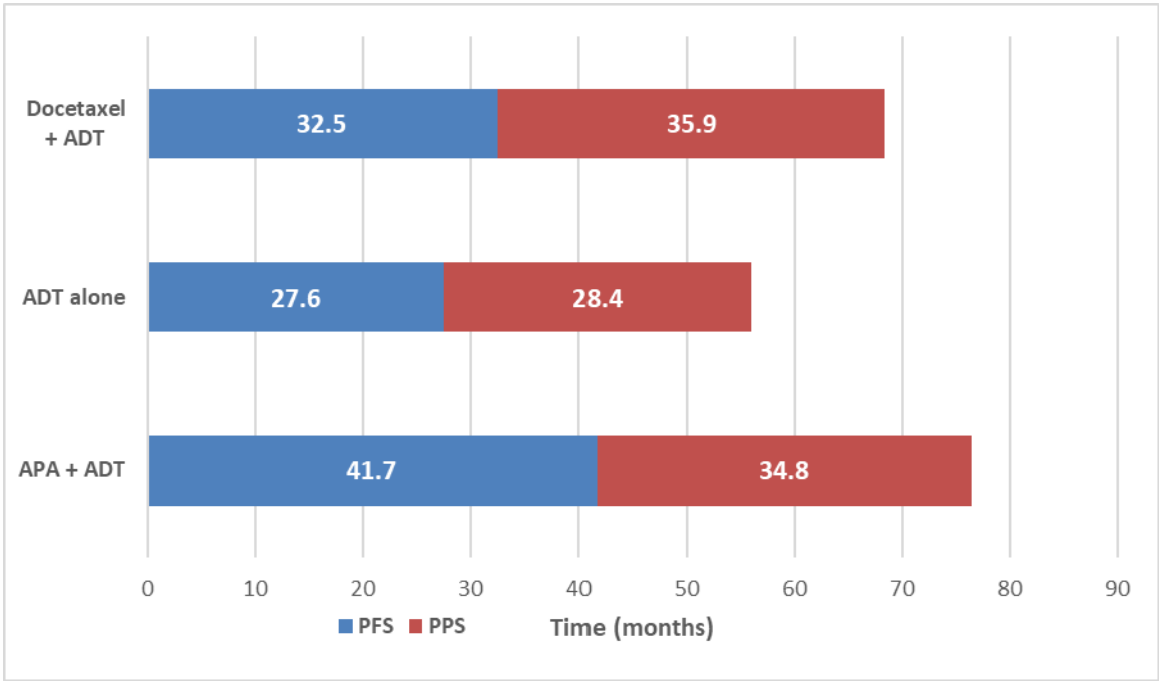
Abbreviations: ADT, androgen deprivation therapy; APA, apalutamide; mHSPC, metastatic hormone-sensitive prostate cancer, nmHRPC, non-metastatic hormone-relapsed prostate cancer

Figure 2. Comparison of life-year before and after progression in company base-case: nmHRPC



Abbreviations: ADT, androgen deprivation therapy; APA, apalutamide; nmHRPC, non-metastatic hormone-relapsed prostate cancer; PFS, progression-free survival; PPS, post-progression survival

Figure 3 Comparison of life-year before and after progression in company base-case: mHSPC



Abbreviations: ADT, androgen deprivation therapy; APA, apalutamide; mHSPC, metastatic hormone-sensitive prostate cancer; PFS, progression-free survival; PPS, post-progression survival

Importantly, feedback from a UK clinical expert in attendance at the committee meeting did note that it was entirely plausible, and even likely that treatment with apalutamide + ADT would result in a significant post-

	progression survival benefit. This assertion was explained with reference to the underlying disease biology and the impact of novel agents received earlier in the treatment pathway. Nonetheless, given that the base-case comparison, in mHSPC, vs ADT alone predicts a small post-progression survival benefit, and the committee specifically requested to see results when post-progression survival was assumed to be equal between the treatment arms, a scenario analysis is presented in Section 7. This scenario was conducted by applying a hazard ratio to the ADT alone extrapolated OS curve, using SOLVER to find the value required to equalise post-progression survival between the arms. The hazard ratio was applied to the ADT alone curve rather than the apalutamide + ADT curve to ensure the comparison of apalutamide + ADT versus docetaxel + ADT remained unchanged. To ensure the time spent in each mHRPC health state was adjusted accordingly, the same hazard ratio was applied to the second progression-free survival (PFS2). The results demonstrate that even if post-progression survival is equalised, apalutamide + ADT remains a cost-effective use of NHS resources. Janssen hopes that this misunderstanding can now be rectified, and that the committee understands the conservative nature of Janssen's economic modelling.
3	**Adjusting for cross-over and second androgen receptor inhibitor** *"The committee concluded that it would like to see:* • *other methods explored in more detail or* • *the uncertainties of the modified RPSFTM approach addressed, such as the costs of treatments not offered in the NHS and unadjusted PFS2 in the COU-AA-302 trial"* [ACD: Section 3.8, p13; Section 3.17, p20] *"Adjusting for crossover from the placebo plus ADT arm to the apalutamide plus ADT arm meant that the company assumed that these people had no treatment after placebo plus ADT. But, in clinical practice, people would likely be offered a novel therapy including abiraterone plus ADT or enzalutamide plus ADT as their first subsequent treatment. However, the committee was aware that people can now have darolutamide plus ADT in the NHS. The committee considered that this part of the company's analysis could have biased against placebo plus ADT. It considered that an analysis that did not adjust survival estimates for crossover could be reasonable"* [ACD: Section 3.11, p15] *"It [the ERG} noted that the treatment in COU-AA-302 had a considerably bigger effect on PFS2 than on overall survival. Therefore, adjusting for PFS2 crossover in COU-AA-302 would have a more pronounced effect on the adjusted hazard ratios and would likely increase the cost-effectiveness estimates. The committee concluded that using the COU-AA-302 data to estimate the effect of a second newer androgen receptor inhibitor and adjust for survival benefit caused uncertainty"* [ACD: Section 3.9, p14] *"The committee noted that COU-AA-302 included only people who had not had a newer androgen receptor inhibitor. So, using these data would 'over adjust' for overall survival of people having a second newer androgen receptor inhibitor"* [ACD: Section 3.10, p14] As noted by the committee, all available methods for adjusting the SPARTAN and TITAN data to increase generalisability to UK clinical practice were investigated. However, the complex nature of the switching seen in SPARTAN and TITAN meant that many of the methods were not viable (rank preserving structural failure time model [RPSFTM], iterative parameter estimator, two-stage) or produced clinically implausible results (inverse probability of censoring weights). As such, the modified RPSFTM approach, using external data to improve reliability of the method, was employed. Janssen understands the committee's concerns regarding uncertainty within the adjustment methods. At this stage in the appraisal, however, it is not feasible to robustly re-explore methods for adjusting for crossover or the use of therapies not permitted in clinical practice. Janssen, therefore, have endeavoured to address the uncertainties of the modified RPSFTM approach, as follows: • the costs of treatments not offered in the NHS;

	• the appropriateness of adjusting for crossover; • the use of unadjusted PFS2 in the COU-AA-302 trial; • the impact of 'over adjusting' for subsequent novel agent use. ***The costs of treatments not offered in the NHS*** As noted in Janssen's original submission (Section B.3.5.2), the selection of subsequent treatments and their sequencing reflects clinical practice in the UK and was based on NICE guidance and expert clinical opinion. The distribution of patients across each subsequent treatment was informed by UK clinical experts at an advisory board and was modelled to be dependent on the treatment received and line of subsequent therapy. It was assumed that patients in metastatic hormone relapsed prostate cancer (mHRPC) received the same set of subsequent therapies for both nmHRPC and mHSPC. In the model base-case, patients could not receive the same treatment twice and subsequent treatments adhered to the NHS England one novel therapy commissioning policy. Janssen, therefore, do not understand the committee's concern regarding *"uncertainties of the modified RPSFTM approach…..such as the costs of treatments not offered in the NHS"*. ***The appropriateness of adjusting for crossover*** Janssen understand the committee's perspective that adjusting for crossover may not be appropriate given that nmHRPC and mHSPC patients may indeed receive a novel agent upon progression. Importantly, crossover in SPARTAN and TITAN was driven by unblinding rather than by progression. Of the patients randomised to the placebo plus ADT arm in SPARTAN, 76 patients (19% of the placebo cohort) crossed over to receive open-label apalutamide after study unblinding and before disease progression.[19, 20] In TITAN, 208 patients (39.5% of those randomised to placebo plus ADT) without disease progression crossed over to receive open-label apalutamide.[20] Janssen, therefore, consider that adjustment for crossover is appropriate. Nonetheless, scenario analyses exploring the impact of unadjusted and adjusted (only for one novel agent restriction and not cross-over) are presented in Section 7. ***The use of unadjusted PFS2 in the COU-AA-302 trial*** It is important to note that progression free survival (PFS) data from COU-AA-302 has been used to adjust PFS2 data from SPARTAN and TITAN (see Appendix R of Document B of Janssen's submission). This is because the COU-AA-302 trial was carried out in mHRPC representing patients who have progressed from nmHRPC or mHSPC. In COU-AA-302, PFS is not impacted by crossover.[21, 22] As such there is no risk of bias from crossover in COU-AA-302 on the adjusted results of SPARTAN or TITAN. ***The impact of 'over adjusting' for subsequent novel agent use*** Janssen agrees with the committee that using COU-AA-302 data may 'over adjust' outcomes for people having a second novel agent. As noted in Janssen's response to technical engagement, the common treatment effect assumption has not been explored. That is, the assumption that patients treated with a second novel agent would experience the same benefit as patients naïve to novel hormone therapy. This assumption is likely to cause bias against apalutamide, as significantly more patients in the apalutamide arm of SPARTAN and of TITAN received a second novel therapy.
4	**The use of flexible modelling** *"The committee concluded that, because of the uncertainty associated with the Weibull model, it would have liked to see a more flexible model fitted"* [ACD: Section 3.22, p23; Section 3.25, p25; Section 3.26, p26] The committee have expressed a preference to see the fitting of more flexible survival curves to model certain survival endpoints. The request for more flexible models in part appears to come from a false understanding of the base-case analyses predictions of post-progression survival (see comment number 2). Additionally, the request seems to be driven by the fact that some of the curves do not align precisely with some of the projections from the clinical experts that consulted with the ERG. Each of the base-case survival curves selected in the company submission, however, were based on extensive clinical feedback

	elicited through a number of advisory boards attended by multiple UK based clinical experts. The clinicians not only assessed the plausibility of the curves in relation to the assumed proportion of patients who were event free at each point in time, but also assessed how the conditional survival probability changed over time for each curve. Each curve selected for the base-case analysis was considered to be plausible by the clinicians, and where there was a level of uncertainty for some of the extrapolations, there was a tendency to select a more pessimistic curve to ensure that the assumed treatment effect was conservative. No standard parametric curve can ever perfectly reflect the estimates of all clinical experts. Moreover, flexible models which are more complex, rely on a larger number of assumptions and still do not guarantee that long-term survival estimates will precisely align with clinical expert estimates. On the use of flexible models, NICE Decision Support Unit Technical Support Document 21 (TSD21) advocates the need to assess whether there are any points where there is a distinct change in the hazard function over time. Assessment of the hazard functions for each endpoint (presented in the original company submission), do not show any indication of the hazards in either treatment arm changing distinctly at any point over time. Similarly, visual inspection of the Kaplan-Meier data also shows there is no indication of the hazard function distinctly changing over time, with patients experiencing PFS, PFS2 and OS events at a relatively constant rate. Therefore, although Janssen acknowledge that the base-case survival curves are simplifications of reality and are therefore imperfect, standard parametric models remain the most appropriate option available to model long-term survival outcomes given no justification for more complex flexible survival modelling approaches exists.
5	**Modelled cost of apalutamide** *"The company explained that the costs used in the model were informed by the minimum of either time-to-treatment discontinuation until progression, or metastases free survival curves. The company therefore capped the costs, which it noted might have slightly underestimated the cost of apalutamide in the model. The committee concluded that cost of apalutamide might have been underestimated in the model, and it would take this into account in its decision making."* [ACD: Section 3.29, p29] The committee have indicated that the cost of treatment with apalutamide was artificially capped and therefore the treatment cost may have been underestimated. Janssen would like to clarify that the time to treatment discontinuation (TTD) and PFS extrapolated curves applied in the model are consistent with the trial data, which show that there was separation between the two curves and that they converge over time. In both the TITAN and SPARTAN trials, the Kaplan-Meier curves did not cross at any point during the studies but because convergence was observed towards the end of the trial period (Figure 4 and Figure 5) this caused some of the extrapolations to cross. However, treatment continuing after progression was not considered feasible based on clinical feedback and contradicts the SmPC, and therefore, time on treatment was modelled based on the minimum of the TTD and PFS extrapolations. **Figure 4. SPARTAN apalutamide Kaplan–Meier curves: MFS and TTD** 

Abbreviations: KM, Kaplan–Meier; MFS, metastases free survival; TTD, time to treatment discontinuation.

Figure 5. TITAN apalutamide Kaplan–Meier curves: rPFS and TTD

Abbreviations: KM, Kaplan–Meier; rPFS, radiographic progression-free survival; TTD, time to treatment discontinuation.

Janssen note, therefore, that the costs observed in the trial are captured fully, and the time on treatment is modelled based on PFS after the trial duration to ensure that both the costs observed during the study periods are fully captured and that long-term time on treatment is modelled appropriately. Moreover, Janssen consider that apalutamide costs may be overestimated as patients can discontinue treatment due to disease progression and also for other reasons. Therefore, by estimating the longer-term treatment costs based on the PFS curve then any discontinuations due to reasons other than progression are no

	longer captured, which if anything would mean that treatment costs may be over-estimated. To allay any remaining concerns, a scenario analysis is presented in Section 7 which models time on treatment based on the PFS curve exclusively. This scenario demonstrates that the results are relatively insensitive to changes in this assumption.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

6. Model Assumptions

nmHRPC - Revised base case

Considering the AC's stated wishes, alongside the issues covered in comments 1-5 of this document, Janssen provide a revised base case, as follows:

- Adjusting for treatment switching and the one novel therapy restriction
- Using unadjusted utility values for second-line and third-line hormone-relapsed metastatic prostate cancer

In addition to the revised base case and in acknowledgement of the AC's request for scenario analyses, Janssen has provided scenario analyses as follows:

- Unadjusted
- Adjusted only for treatment switching and not cross-over
- Time on treatment equal to PFS

Scenario analyses using alternative methods to adjust and a more flexible method to extrapolate metastases-free survival have not been explored for reasons outlined in comments 3 and 4.

mHSPC - Revised base case

Considering the AC's stated wishes, alongside the issues covered in comments 1-5 of this document, Janssen provide a revised base case, as follows:

- Using unadjusted utility values for second-line and third-line metastatic disease reported in TA377
- Using pooled incidence rates for neutropenia (15.4%) and febrile neutropenia (10.6%; see section 3.32 of ACD)
- Using the gompertz extrapolation to model PFS2
- Adjusting for treatment switching and the one novel therapy restriction

In addition to the revised base case and in acknowledgement of the AC's request for scenario analyses, Janssen has provided scenario analyses as follows:

- Unadjusted
- Adjusted only for treatment switching and not cross-over
- Assume equal post-progression survival
- Set time on treatment equal to PFS
- Removing chemotherapy as a subsequent treatment
- Reducing the utility values by a decrement of 0.1
- Unadjusted subgroup analyses in locally advanced/primary progressive patients, low volume patients and chemotherapy-unsuitable patients

Scenario analyses using alternative methods to adjust and more flexible methods for extrapolating radiographic progression-free survival, overall survival and PFS2 have not been explored for reasons outlined in comments 3 and 4.

7. Revised economic analyses

An updated confidential patient access scheme (PAS) has been submitted and is expected to be approved prior to the second appraisal committee meeting. This arrangement provides apalutamide to NHS patients at a [redacted]% discount on list price. Therefore, this PAS has been applied and the results presented reflect this discount.

Table 3 summarises the revised company base case for nmHRPC, incorporating committee preferred assumptions plus additional scenario analyses requested in the ACD. The revised company base-case for nmHRPC is presented in Table 4. Probabilistic scatterplot is presented in **Error! Reference source not found.**.

Table 3. Updated cost-effectiveness results for nmHRPC (% discount applied)

Scenario	Results vs ADT alone		
	Inc. costs	Inc. QALYs	ICER
Post technical engagement company base-case (including updated PAS discount of %)			-£4,125 (Dominant)
Apply unadjusted utility values for 2L & 3L and mHRPC reported in TA377			-£4,586 (Dominant)
Company revised base-case			-£4,586 (Dominant)
Additional scenarios (applied to the company revised base-case)			
Unadjusted			-£3,615 (Dominant)
Adjusted only for treatment switching and not cross-over			-£9,552 (Dominant)
Set time on treatment equal to PFS			-£143 (Dominant)

Abbreviations: 2L, second-line; 3L, third-line; ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; Inc, incremental; mHRPC, metastatic hormone relapsed prostate cancer; nmHRPC, non-metastatic hormone-relapsed prostate cancer; PAS, patient access scheme; PFS, progression free survival; QALYs, quality-adjusted life years

Table 4. Revised company base-case results, nmHRPC, apalutamide plus ADT vs ADT alone including % PAS discount

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Deterministic							
ADT alone		5.50					
Apalutamide plus ADT		6.26			0.76		-£4,586 (Dominates)
Probabilistic							
ADT alone		5.50					
Apalutamide plus ADT		6.26			0.76		-£5,042 (Dominates)

Abbreviations: ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; Inc, incremental; nmHRPC, non-metastatic hormone-relapsed prostate cancer; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years

Table 5 summarises the revised company base case for mHSPC, incorporating committee preferred assumptions plus additional scenario analyses requested in the ACD. The fully incremental revised company base-case for mHSPC is presented in

Table 6, with revised company base case for patients who do not currently receive chemotherapy presented in Table 7. Probabilistic scatterplots are presented in **Error! Reference source not found.** and **Error! Reference source not found.**. Additional scenario analyses in subgroups of patients who do not currently receive treatment with docetaxel are presented in Table 8.

Table 5. Updated cost-effectiveness results for mHSPC ([redacted]% discount applied)

	Results vs ADT alone			Results vs docetaxel + ADT		
Scenario	**Inc costs**	**Inc QALYs**	**ICER**	**Inc costs**	**Inc QALYs**	**ICER**
Post technical engagement company base-case (including updated PAS discount of [redacted]%)	[redacted]	[redacted]	£8,060	[redacted]	[redacted]	£3,901
Apply unadjusted utility values for 2L & 3L and mHRPC reported in TA377	[redacted]	[redacted]	£8,233	[redacted]	[redacted]	£4,633
Using pooled incidence rates for neutropenia (15.4%) and febrile neutropenia (10.6%)	[redacted]	[redacted]	£8,060	[redacted]	[redacted]	£4,798
Using the gompertz extrapolation to model PFS2	[redacted]	[redacted]	£11,545	[redacted]	[redacted]	£11,420
Adjusted	[redacted]	[redacted]	£12,576	[redacted]	[redacted]	£6,532
Company revised base-case	[redacted]	[redacted]	£16,322	[redacted]	[redacted]	£19,211
Additional scenarios (applied to the company revised base-case)						
Unadjusted	[redacted]	[redacted]	£11,153	[redacted]	[redacted]	£14,574
Adjusted only for treatment switching and not cross-over	[redacted]	[redacted]	£10,573	[redacted]	[redacted]	£12,560
Assume equal post-progression survival	[redacted]	[redacted]	£14,386	[redacted]	[redacted]	N/A
Set time on treatment equal to PFS	[redacted]	[redacted]	£17,180	[redacted]	[redacted]	£21,149
Removing chemotherapy as a subsequent treatment	[redacted]	[redacted]	£13,161	[redacted]	[redacted]	N/A
Reducing the utility values by a decrement of 0.1	[redacted]	[redacted]	£18,134	[redacted]	[redacted]	N/A

Abbreviations: 2L, second-line; 3L, third-line; ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; Inc, incremental; mHRPC, metastatic hormone relapsed prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer; PAS, patient access scheme; PFS, progression free survival; PFS2, second progression free survival; QALYs, quality-adjusted life years

Table 6. Revised company base-case, mHSPC, fully incremental results for docetaxel eligible patients including [redacted]% PAS discount

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Deterministic							
ADT alone	[redacted]	4.66	[redacted]				
Docetaxel plus ADT	[redacted]	5.70	[redacted]	[redacted]	1.03	[redacted]	Extendedly dominated
Apalutamide plus ADT	[redacted]	6.38	[redacted]	[redacted]	0.68	[redacted]	£16,322
Probabilistic							
ADT alone	[redacted]	4.66	[redacted]				
Docetaxel plus ADT	[redacted]	5.69	[redacted]	[redacted]	1.03	[redacted]	£11,535
Apalutamide plus ADT	[redacted]	6.38	[redacted]	[redacted]	0.68	[redacted]	£21,662

Abbreviations: ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; Inc, incremental; mHSPC, metastatic hormone-sensitive prostate cancer; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years

Table 7. Revised company base-case results, mHSPC, docetaxel ineligible patients including [redacted]% PAS discount

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Deterministic							
ADT alone	[redacted]	4.66	[redacted]				
Apalutamide plus ADT	[redacted]	6.38	[redacted]	[redacted]	1.71	[redacted]	£16,322
Probabilistic							
ADT alone	[redacted]	4.66	[redacted]				
Apalutamide plus ADT	[redacted]	6.38	[redacted]	[redacted]	1.71	[redacted]	£16,099

Abbreviations: ADT, androgen deprivation therapy; ICER, incremental cost-effectiveness ratio; Inc, incremental; mHSPC, metastatic hormone-sensitive prostate cancer; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years

Apalutamide for treating prostate cancer [ID1534]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Friday 11 June 2021 email:** NICE DOCS

Table 8. Scenario analyses in patients who do not currently receive docetaxel, mHSPC, apalutamide plus ADT vs ADT alone (XX% discount applied)

Subgroup	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Full population	[redacted]	[redacted]	£11,153
Metastasis stage at diagnosis of M0	[redacted]	[redacted]	£21,881
Low volume disease	[redacted]	[redacted]	£30,680
ECOG 1	[redacted]	[redacted]	£10,506
Age >75	[redacted]	[redacted]	£23,379
ECOG & age >75	[redacted]	[redacted]	£14,749
Note: *The AC's preferred assumptions are maintained in each scenario with the exception of using adjusted data, unadjusted data are employed*			

Abbreviations: AC, Appraisal Committee; ADT, androgen deprivation therapy; ECOG, Eastern Cooperative Oncology Group; ICER: incremental cost-effectiveness ratio; Inc, incremental; M0, non-metastatic; mHSPC, metastatic hormone sensitive prostate cancer; QALY: quality-adjusted life year

Appendix A

A summary of the clinical outcomes for each of the subgroups for patients who currently do not receive docetaxel is presented in Table 9 for OS, Table 10 for rPFS and Table 11 for PFS2. Results for the ITT population are also presented for each of the outcomes for comparison. The subgroup results show consistency with the ITT or overall study results.

Table 9. Summary of OS per subgroup in the TITAN trial (Final analysis; clinical cut-off date 7th September 2020)

Population	Measure	Apalutamide plus ADT	Placebo plus ADT	Treatment effect (apalutamide plus ADT vs placebo plus ADT)
ITT	Number of patients	525	527	HR[a]: 0.65
	Event, n (%)	170 (32.4%)	235 (44.6%)	95% CI: 0.53, 0.79
	Censored, n (%)	355 (67.6%)	292 (55.4%)	p < 0.0001
	Median, months	NE (NE, NE)	52.2 (41.9, NE)	
Metastasis stage at diagnosis is M0	Number of patients	[redacted]	[redacted]	[redacted]
	Event, n (%)	[redacted]	[redacted]	
	Censored, n (%)	[redacted]	[redacted]	
	Median, months	[redacted]	[redacted]	
Low volume disease	Number of patients	[redacted]	[redacted]	[redacted]
	Event, n (%)	[redacted]	[redacted]	
	Censored, n (%)	[redacted]	[redacted]	
	Median, months	[redacted]	[redacted]	
Age>75 and ECOG =1	Number of patients	[redacted]	[redacted]	[redacted]
	Event, n (%)	[redacted]	[redacted]	
	Censored, n (%)	[redacted]	[redacted]	
	Median, months	[redacted]	[redacted]	
Age>75	Number of patients	[redacted]	[redacted]	[redacted]
	Event, n (%)	[redacted]	[redacted]	
	Censored, n (%)	[redacted]	[redacted]	
	Median, months	[redacted]	[redacted]	
ECOG =1	Number of patients	[redacted]	[redacted]	[redacted]
	Event, n (%)	[redacted]	[redacted]	
	Censored, n (%)	[redacted]	[redacted]	
	Median, months	[redacted]	[redacted]	

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; ECOG; Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intention to treat; NE, not estimable; NR, not reached; OS, overall survival

[a] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favours active treatment

Table 10. Summary of rPFS per subgroup in the TITAN trial (Final analysis; clinical cut-off date 7th September 2020)

Population	Measure	Apalutamide plus ADT	Placebo plus ADT	Treatment effect (apalutamide plus ADT vs placebo plus ADT)
ITT	Number of patients	525	527	HR[a]: 0.48
	Event, n (%)	134 (25.5%)	231 (43.8%)	95% CI: 0.39, 0.60
	Censored, n (%)	391 (74.5%)	296 (56.2%)	p < 0.0001
	Median, months	NE (NE, NE)	22.08 (18.5, 32.9%)	
Metastasis stage at diagnosis is M0	Number of patients	[redacted]	[redacted]	[redacted]
	Event, n (%)	[redacted]	[redacted]	
	Censored, n (%)	[redacted]	[redacted]	
	Median, months	[redacted]	[redacted]	
Low volume disease	Number of patients	[redacted]	[redacted]	[redacted]
	Event, n (%)	[redacted]	[redacted]	
	Censored, n (%)	[redacted]	[redacted]	
	Median, months	[redacted]	[redacted]	
Age>75 and ECOG =1	Number of patients	[redacted]	[redacted]	[redacted]
	Event, n (%)	[redacted]	[redacted]	
	Censored, n (%)	[redacted]	[redacted]	
	Median, months	[redacted]	[redacted]	
Age>75	Number of patients	[redacted]	[redacted]	[redacted]
	Event, n (%)	[redacted]	[redacted]	
	Censored, n (%)	[redacted]	[redacted]	
	Median, months	[redacted]	[redacted]	
ECOG =1	Number of patients	[redacted]	[redacted]	[redacted]
	Event, n (%)	[redacted]	[redacted]	
	Censored, n (%)	[redacted]	[redacted]	
	Median, months	[redacted]	[redacted]	

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; ECOG; Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intention to treat; NE, not estimable; NR, not reached; rPFS, radiographic progression-free survival

[a] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favours active treatment

Table 11. Summary of PFS2 per subgroup in the TITAN trial (Final analysis; clinical cut-off date 7th September 2020)

Population	Measure	Apalutamide plus ADT	Placebo plus ADT	Treatment effect (apalutamide plus ADT vs placebo plus ADT)
ITT	Number of patients	525	527	HR[a]: 0.66
	Event, n (%)	153 (29.1%)	200 (38.0%)	95% CI: 0.53, 0.81
	Censored, n (%)	372 (70.9%)	327 (62.1%)	P < 0.0001
	Median, months	NE (NE, NE)	NE (45.77, NE)	
Metastasis stage at diagnosis is M0	Number of patients	[redacted]	[redacted]	[redacted]
	Event, n (%)	[redacted]	[redacted]	
	Censored, n (%)	[redacted]	[redacted]	
	Median, months	[redacted]	[redacted]	
Low volume disease	Number of patients	[redacted]	[redacted]	[redacted]
	Event, n (%)	[redacted]	[redacted]	
	Censored, n (%)	[redacted]	[redacted]	
	Median, months	[redacted]	[redacted]	
Age>75 and ECOG =1	Number of patients	[redacted]	[redacted]	[redacted]
	Event, n (%)	[redacted]	[redacted]	
	Censored, n (%)	[redacted]	[redacted]	
	Median, months	[redacted]	[redacted]	
Age>75	Number of patients	[redacted]	[redacted]	[redacted]
	Event, n (%)	[redacted]	[redacted]	
	Censored, n (%)	[redacted]	[redacted]	
	Median, months	[redacted]	[redacted]	
ECOG =1	Number of patients	[redacted]	[redacted]	[redacted]
	Event, n (%)	[redacted]	[redacted]	
	Censored, n (%)	[redacted]	[redacted]	
	Median, months	[redacted]	[redacted]	

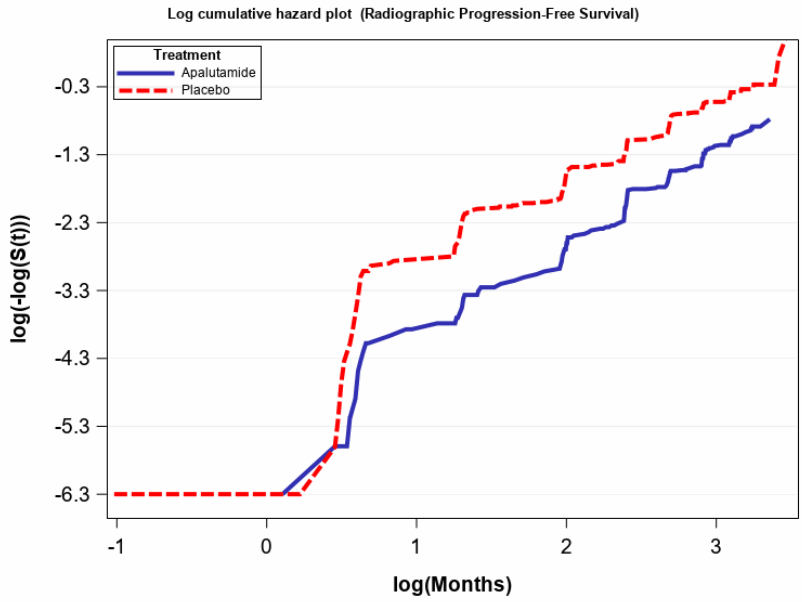
Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; ECOG; Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intention to treat; NE, not estimable; NR, not reached; PFS2, second progression-free survival

[a] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favours active treatment

Appendix B

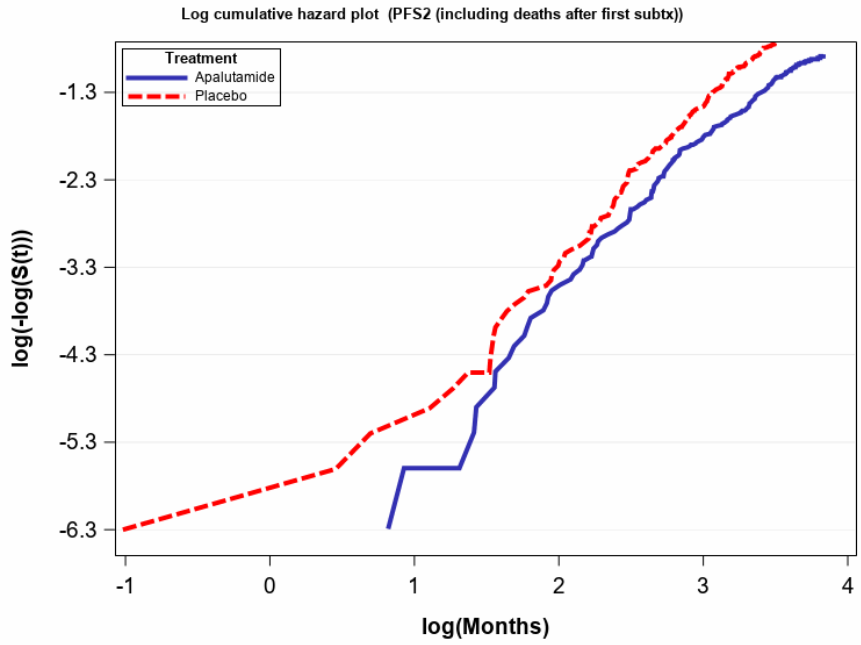
TITAN ITT population log-cumulative hazard plots

Figure 6. Log-cumulative hazard plots (TITAN: rPFS)



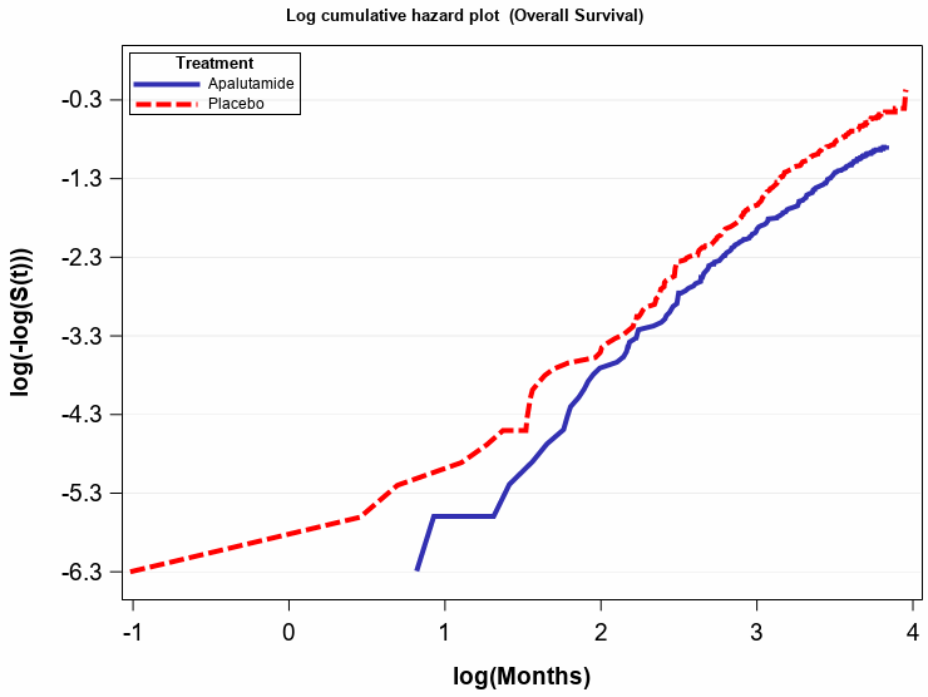
Abbreviations: rPFS, radiographic progression-free survival

Figure 7. Log-cumulative hazard plots (TITAN: PFS2)



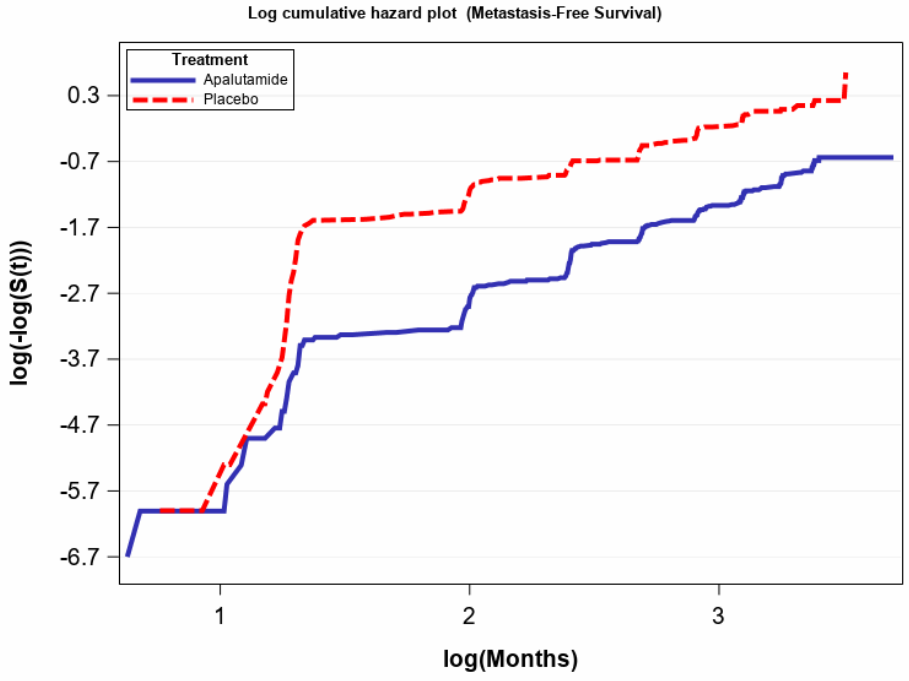
Abbreviations: PFS2, second progression-free survival

Figure 8. Log-cumulative hazard plots (TITAN: OS)



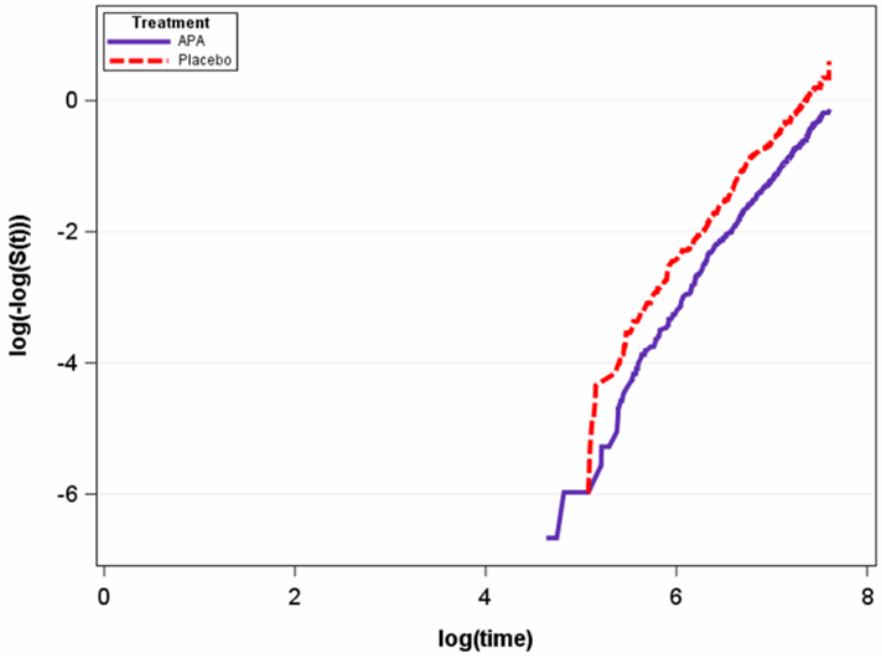
Abbreviations: OS, overall survival

Figure 9. Log-cumulative hazard plots (SPARTAN: MFS)



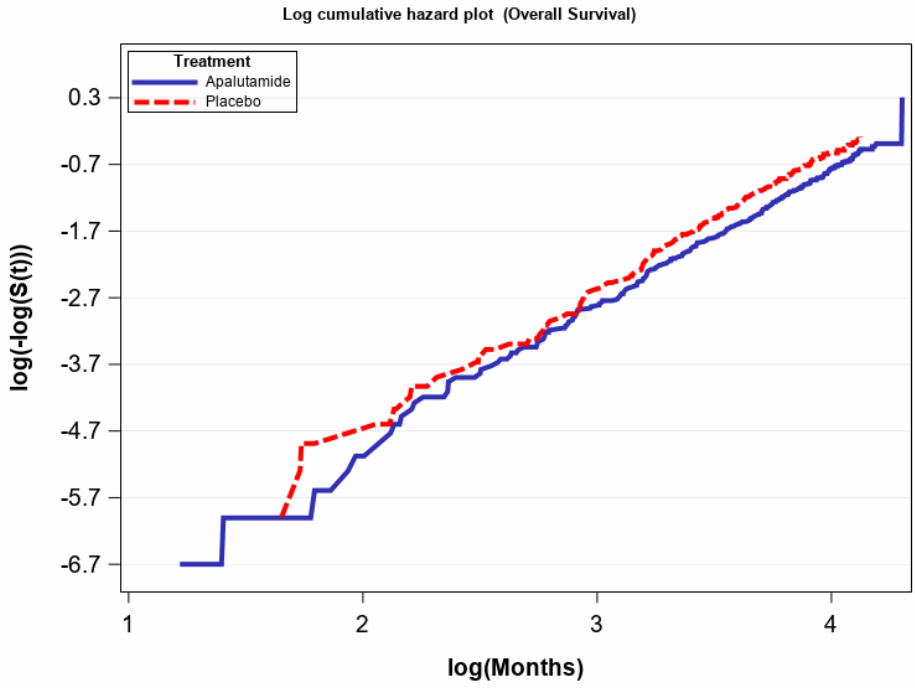
Abbreviations: MFS, metastases-free survival

Figure 10. Log-cumulative hazard plots (SPARTAN: PFS2)



Abbreviations: PFS2, second progression-free survival

Figure 11. Log-cumulative hazard plots (SPARTAN: OS)



Abbreviations: OS, overall survival

TITAN sub-group survival extrapolations

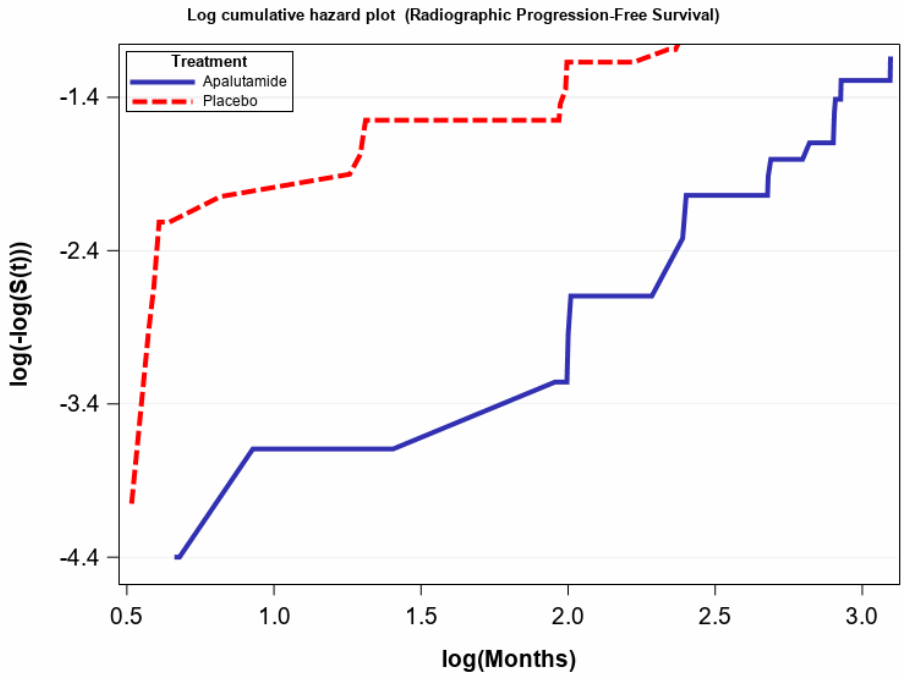
Locally advanced sub-group

Figure 12. TTD extrapolation: apalutamide + ADT (TITAN, locally advanced sub-group)

	AIC	BIC
Weibull	421.6	426.4
Gompertz	421.6	426.5
Log-logistic	421.4	426.3
Log-normal	424.6	429.5
Gen gamma	423.5	430.9
Exponential	424.5	426.9

Abbreviations: ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; TTD, time to treatment discontinuation

Figure 13. Log-cumulative hazard plots (TITAN, locally advanced sub-group, rPFS)



Abbreviations: rPFS, radiographic progression-free survival

Figure 14. rPFS extrapolation: apalutamide + ADT (TITAN, locally advanced sub-group, stratified curves)

[redacted]

	AIC	BIC
Weibull	185.2	190.1
Gompertz	186.3	191.2
Log-logistic	185	189.9
Log-normal	185.3	190.1
Gen gamma	187	194.4
Exponential	186.3	188.8

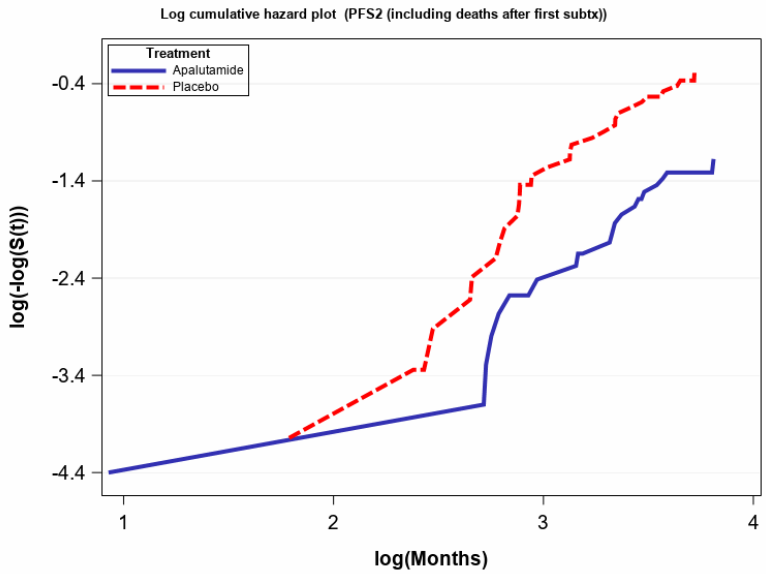
Abbreviations: ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; rPFS, radiographic progression-free survival

Figure 15. PFS extrapolation: ADT alone (TITAN, locally advanced sub-group, stratified curves)

	AIC	BIC
Weibull	212	216.2
Gompertz	209.9	214
Log-logistic	210.6	214.7
Log-normal	208.5	212.7
Gen gamma	204.6	210.8
Exponential	210.5	212.5

Abbreviations: ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; rPFS, radiographic progression-free survival

Figure 16. Log-cumulative hazard plots (TITAN, locally advanced sub-group, PFS2)



Abbreviations: PFS2, second progression-free survival

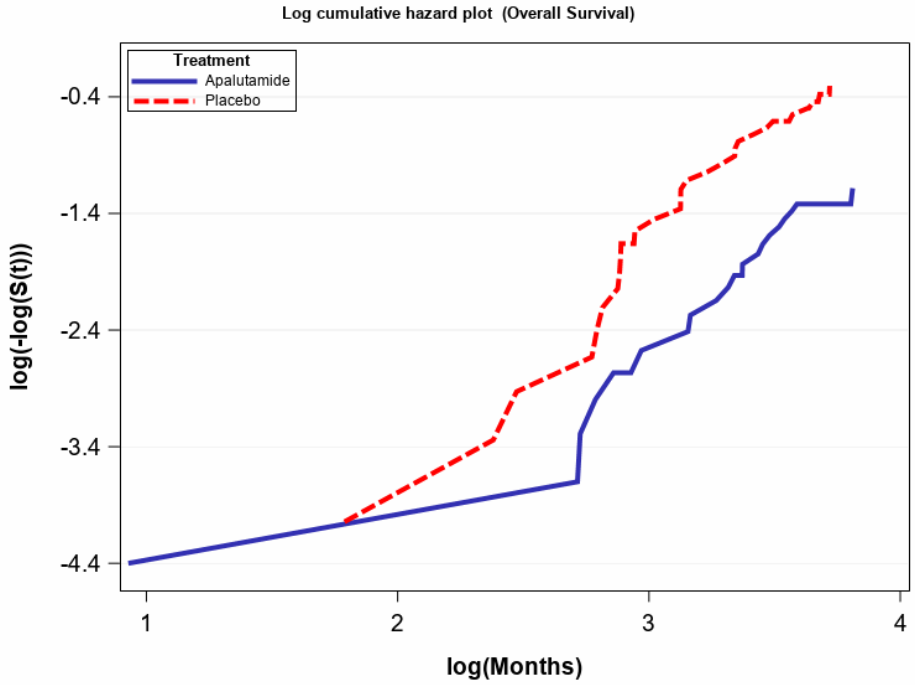
Figure 17. PFS2 extrapolation: apalutamide + ADT & ADT alone (TITAN, locally advanced sub-group, unstratified curves)

[redacted]

	AIC	BIC
Weibull	538	546.9
Gompertz	544.6	553.5
Log-logistic	535.7	544.6
Log-normal	536.5	545.4
Gen gamma	537.9	549.8

Exponential	549	554.9

Figure 18. Log-cumulative hazard plots (TITAN, locally advanced sub-group, OS)



Abbreviations: OS, overall survival

Figure 19. OS extrapolation: apalutamide + ADT & ADT alone (TITAN, locally advanced sub-group, unstratified curves)

	AIC	BIC
Weibull	538.2	547.1
Gompertz	544.7	553.6
Log-logistic	536.3	545.3
Log-normal	538.1	547
Gen gamma	538.8	550.7
Exponential	551.5	557.5

Abbreviations: ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival

Low volume sub-group

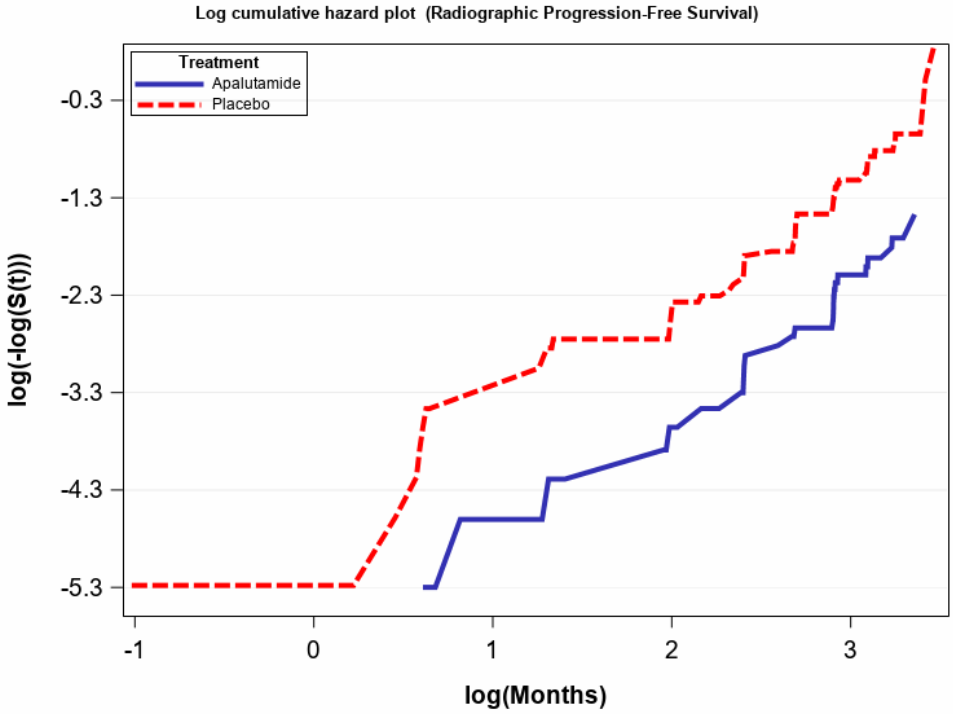
Figure 20. TTD extrapolation: apalutamide + ADT (TITAN, low volume sub-group)

[redacted]

	AIC	BIC
Weibull	737.0	743.6
Gompertz	738.5	745.1
Log-logistic	736.9	743.5
Log-normal	741.0	747.6
Gen gamma	738.9	748.8
Exponential	743.6	746.9

Abbreviations: ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; TTD, time to treatment discontinuation

Figure 21. Log-cumulative hazard plots (TITAN, low volume sub-group, rPFS)



Abbreviations: rPFS, radiographic progression-free survival

Figure 22. rPFS extrapolation: apalutamide + ADT (TITAN, low volume sub-group, stratified curves)

[redacted]

	AIC	BIC
Weibull	299.4	306
Gompertz	299.4	306
Log-logistic	299.6	306.2
Log-normal	301.2	307.8
Gen gamma	301.3	311.2
Exponential	303.8	307.1

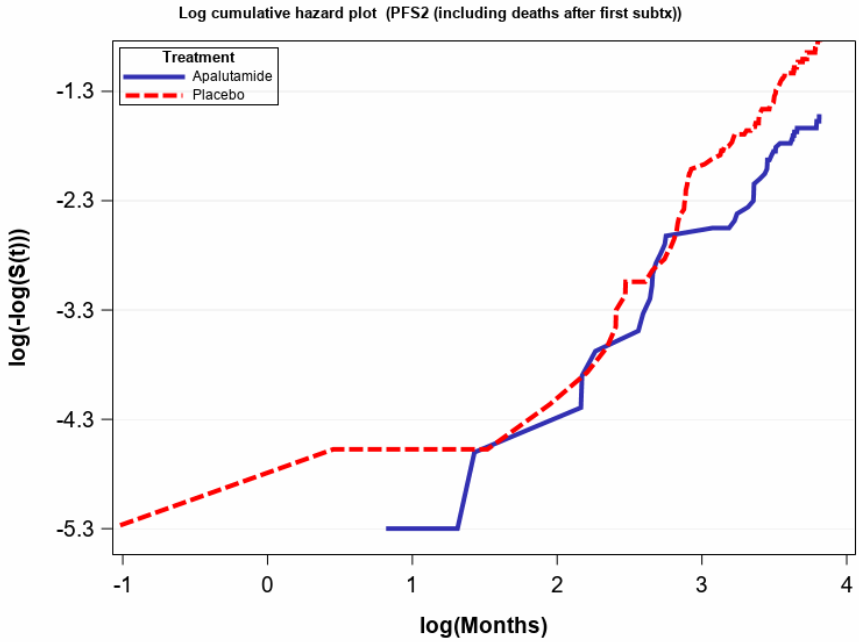
Abbreviations: ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; rPFS, radiographic progression-free survival

Figure 23. rPFS extrapolation: ADT alone (TITAN, low volume sub-group, stratified curves)

	AIC	BIC
Weibull	582.4	588.9
Gompertz	578.9	585.4
Log-logistic	585	591.5
Log-normal	591	597.5
Gen gamma	581.4	591.2
Exponential	587.8	591

Abbreviations: ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; rPFS, radiographic progression-free survival

Figure 24. Log-cumulative hazard plots (TITAN, low volume sub-group, PFS2)



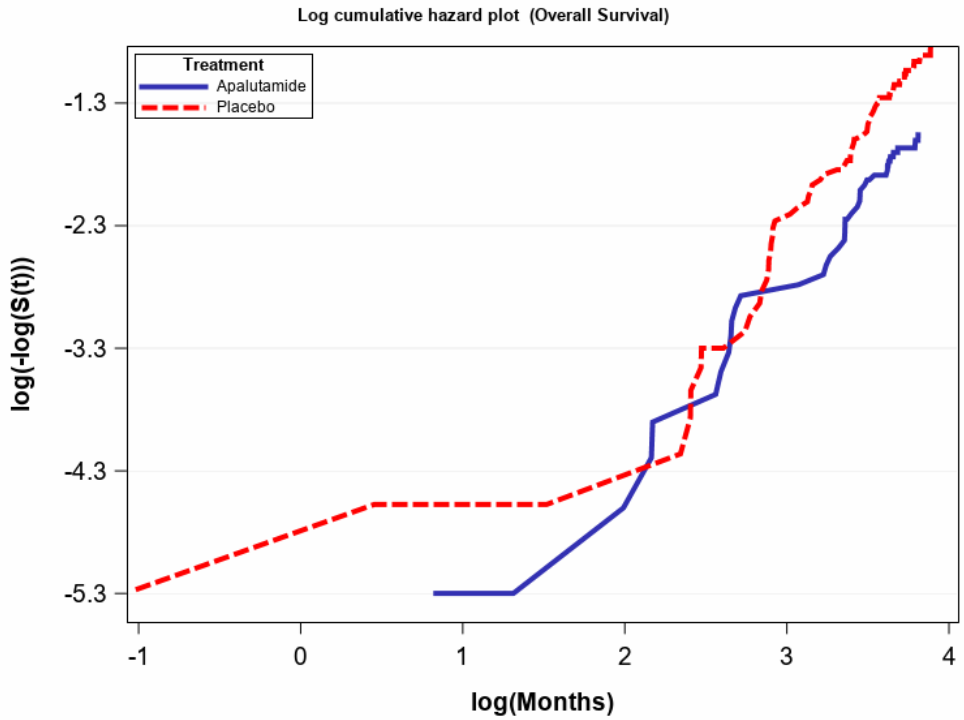
Abbreviations: PFS2, second progression-free survival

Figure 25. PFS2 extrapolation: apalutamide + ADT & ADT alone (TITAN, low volume sub-group, unstratified curves)

[redacted]

	AIC	BIC
Weibull	1,182.30	1,194.20
Gompertz	1,186.30	1,198.20
Log-logistic	1,182.60	1,194.60
Log-normal	1,191.20	1,203.10
Gen gamma	1184.3	1,200.20
Exponential	1,196.50	1,204.40

Figure 26. Log-cumulative hazard plots (TITAN, low volume sub-group, OS)



Abbreviations: OS, overall survival

Figure 27. OS extrapolation: apalutamide + ADT & ADT alone (TITAN, low volume sub-group, unstratified curves)

	AIC	BIC
Weibull	1,144.10	1,156.00
Gompertz	1,146.90	1,158.90
Log-logistic	1144.7	1,156.60
Log-normal	1,155.80	1,167.80
Gen gamma	1,145.90	1,161.80
Exponential	1,163.40	1,171.30

Abbreviations: ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival

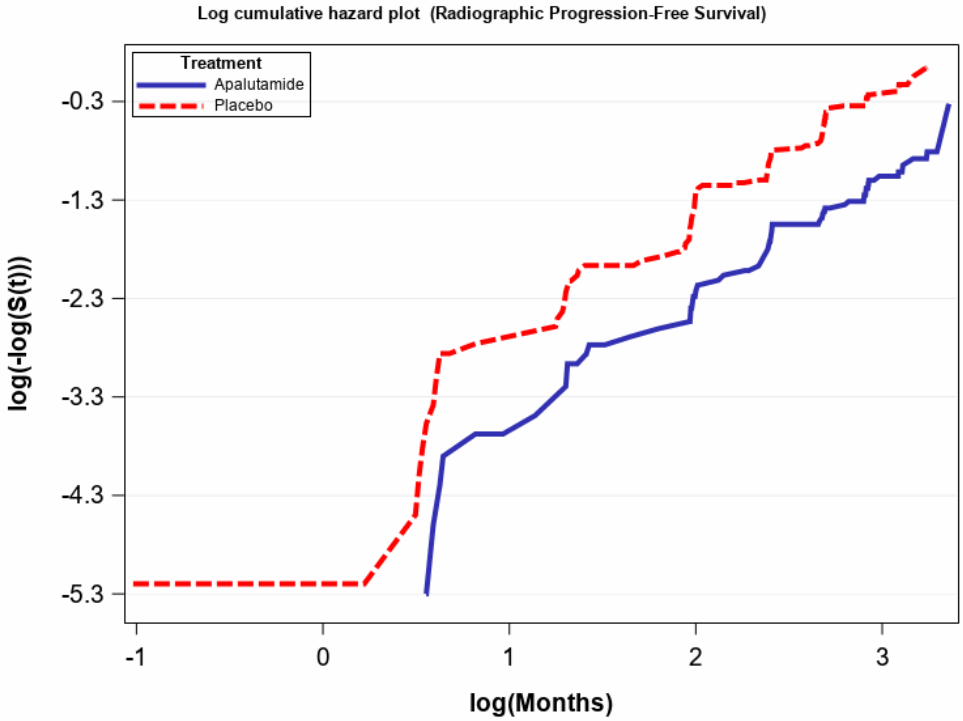
ECOG 1 sub-group

Figure 28. TTD extrapolation: apalutamide + ADT (TITAN, ECOG 1 sub-group)

	AIC	BIC
Weibull	1076.8	1083.3
Gompertz	1073.7	1080.3
Log-logistic	1072.6	1079.2
Log-normal	1072.7	1079.3
Gen gamma	1074.3	1084.2
Exponential	1075.6	1078.8

Abbreviations: ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; ECOG, Eastern Co-operative Oncology Group; TTD, time to treatment discontinuation

Figure 29. Log-cumulative hazard plots (TITAN, ECOG 1 sub-group, rPFS)



Abbreviations: rPFS, radiographic progression-free survival

Figure 30. rPFS extrapolation: apalutamide + ADT (TITAN, ECOG 1 sub-group, stratified curves)

[redacted]

	AIC	BIC
Weibull	558.3	564.8

Gompertz	560.3	566.8
Log-logistic	557.7	564.3
Log-normal	556.3	562.9
Gen gamma	561.1	571
Exponential	560.2	563.4

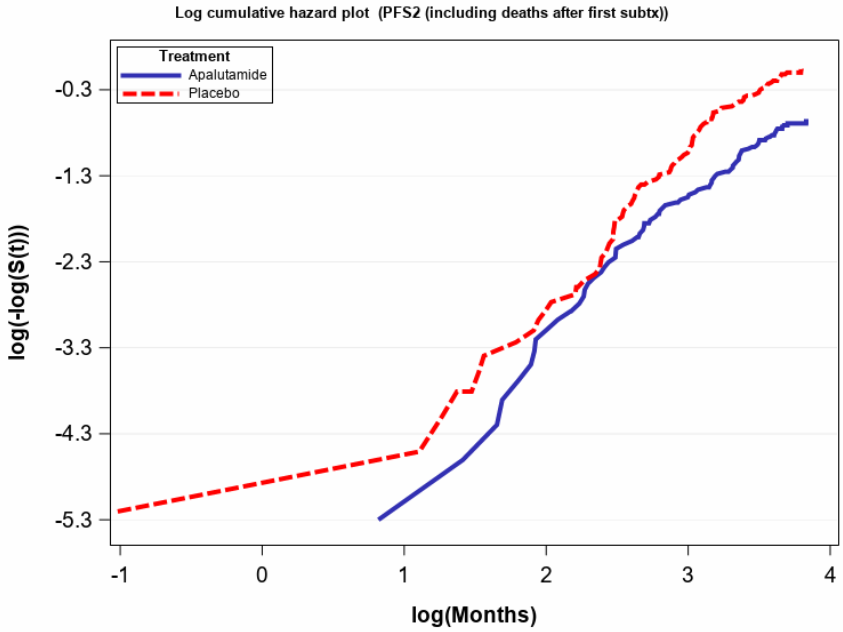
Abbreviations: ADT, androgen deprivatio therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; ECOG, Eastern Co-operative Oncology Group; rPFS, radiographic progression-free survival

Figure 31. rPFS extrapolation: ADT alone (TITAN, ECOG 1 sub-group, stratified curves)

	AIC	BIC
Weibull	754	760.4
Gompertz	757.8	764.2
Log-logistic	751.9	758.3
Log-normal	752.5	758.9
Gen gamma	753.6	763.2
Exponential	758	761.2

Abbreviations: ADT, androgen deprivatio therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; ECOG, Eastern Co-operative Oncology Group; rPFS, radiographic progression-free survival

Figure 32. Log-cumulative hazard plots (TITAN, ECOG 1 sub-group, PFS2)



Abbreviations: ECOG, Eastern Co-operative Oncology Group; PFS2, second progression-free survival

Figure 33. PFS2 extrapolation: apalutamide + ADT & ADT alone (TITAN, ECOG 1 sub-group, unstratified curves)

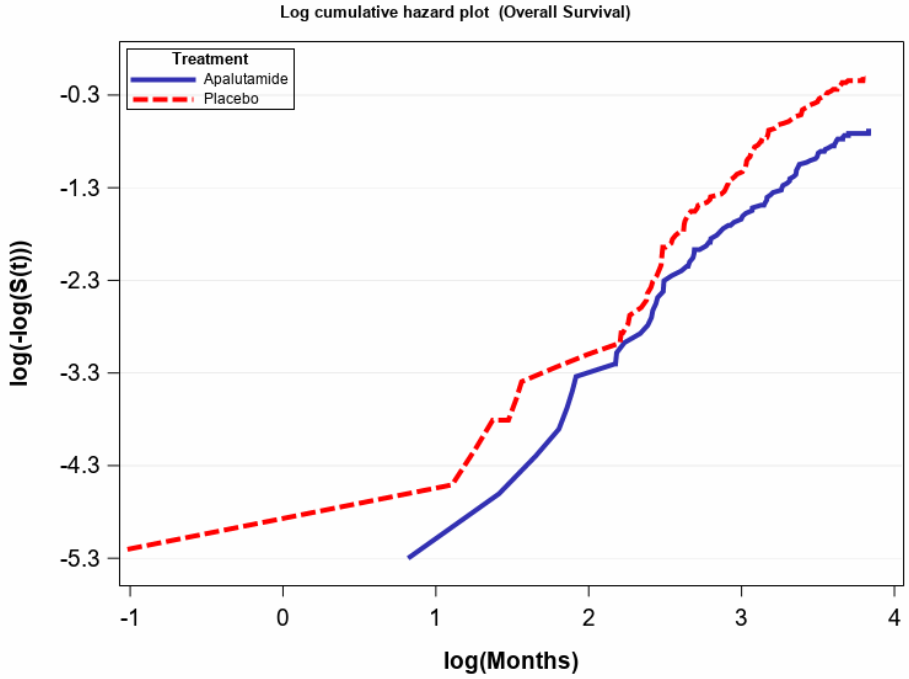
[redacted]

	AIC	BIC

Weibull	1,836.30	1,848.00
Gompertz	1,849.50	1,861.30
Log-logistic	1,826.40	1,838.20
Log-normal	1,826.90	1,838.70
Gen gamma	1828.3	1,844.00
Exponential	1,851.10	1,858.90

Abbreviations: ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; ECOG, Eastern Co-operative Oncology Group; PFS2, second progression-free survival

Figure 34. Log-cumulative hazard plots (TITAN, ECOG 1 sub-group, OS)



Abbreviations: OS, overall survival

Figure 35. OS extrapolation: apalutamide + ADT & ADT alone (TITAN, ECOG 1 sub-group, unstratified curves)

	AIC	BIC
Weibull	1,817.20	1,828.90
Gompertz	1,831.90	1,843.60
Log-logistic	1808.3	1,820.10
Log-normal	1,810.70	1,822.50
Gen gamma	1,811.20	1,826.90
Exponential	1,836.30	1,844.10

Abbreviations: ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; ECOG, Eastern Co-operative Oncology Group; OS, overall survival

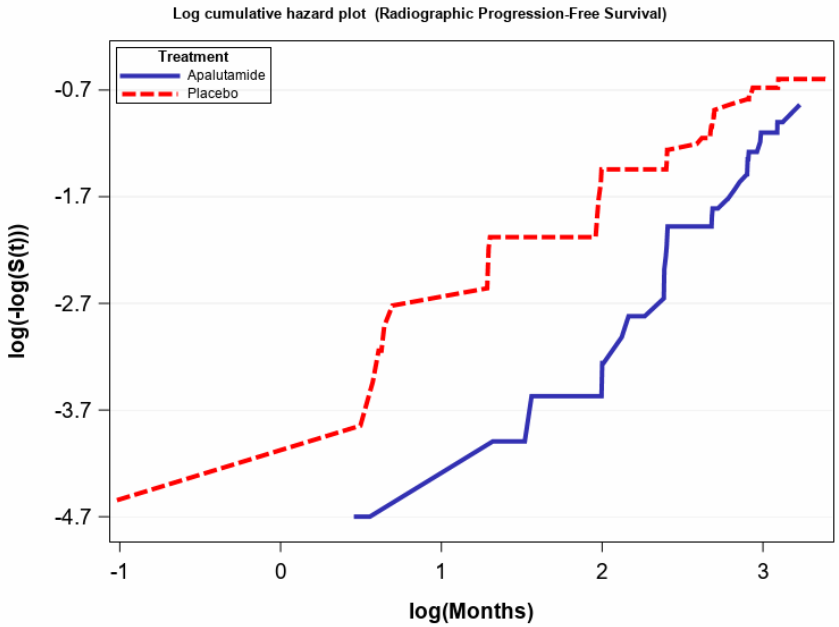
Over 75 sub-group

Figure 36. TTD extrapolation: apalutamide + ADT (TITAN, over 75 sub-group)

	AIC	BIC
Weibull	622.5	627.9
Gompertz	622.4	627.8
Log-logistic	621.0	626.4
Log-normal	623.2	628.7
Gen gamma	623.4	631.6
Exponential	620.6	623.3

Abbreviations: ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; TTD, time to treatment discontinuation

Figure 37. Log-cumulative hazard plots (TITAN, over 75 sub-group, rPFS)



Abbreviations: rPFS, radiographic progression-free survival

Figure 38. PFS extrapolation: apalutamide + ADT (TITAN, over 75 sub-group, stratified curves)

[redacted]

	AIC	BIC
Weibull	269.5	274.9
Gompertz	271.4	276.8
Log-logistic	269.4	274.9
Log-normal	270.9	276.3
Gen gamma	271.5	279.7
Exponential	277.3	280

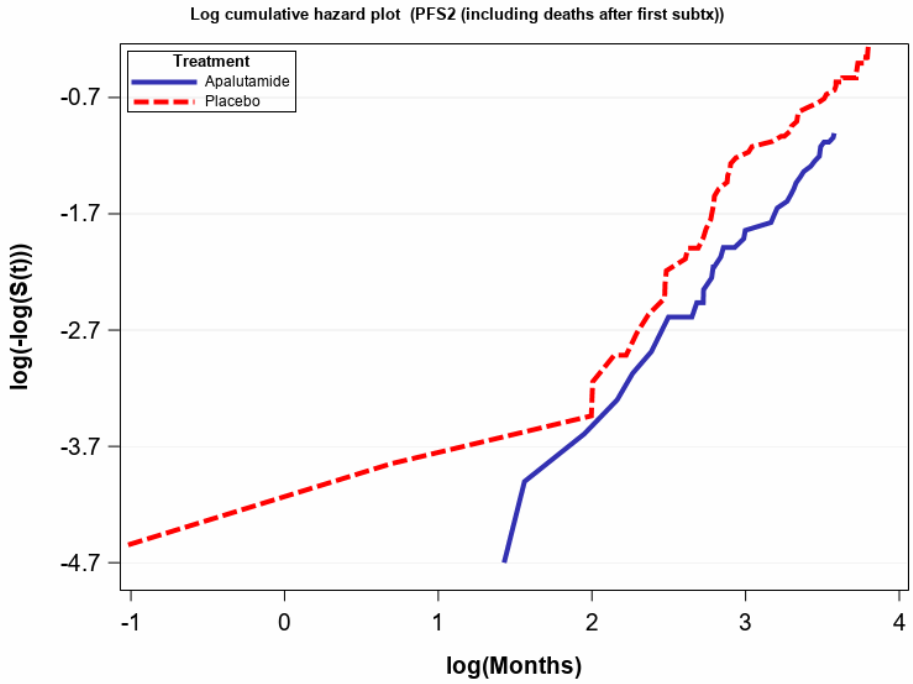
Abbreviations: ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; rPFS, radiographic progression-free survival

Figure 39. rPFS extrapolation: ADT alone (TITAN, over 75 sub-group, stratified curves)

	AIC	BIC
Weibull	335.6	340.7
Gompertz	335.6	340.8
Log-logistic	335.3	340.4
Log-normal	335.2	340.3
Gen gamma	337	344.7
Exponential	333.6	336.2

Abbreviations: ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; rPFS, radiographic progression-free survival

Figure 40. Log-cumulative hazard plots (TITAN, over 75 sub-group, PFS2)



Abbreviations: PFS2, second progression-free survival

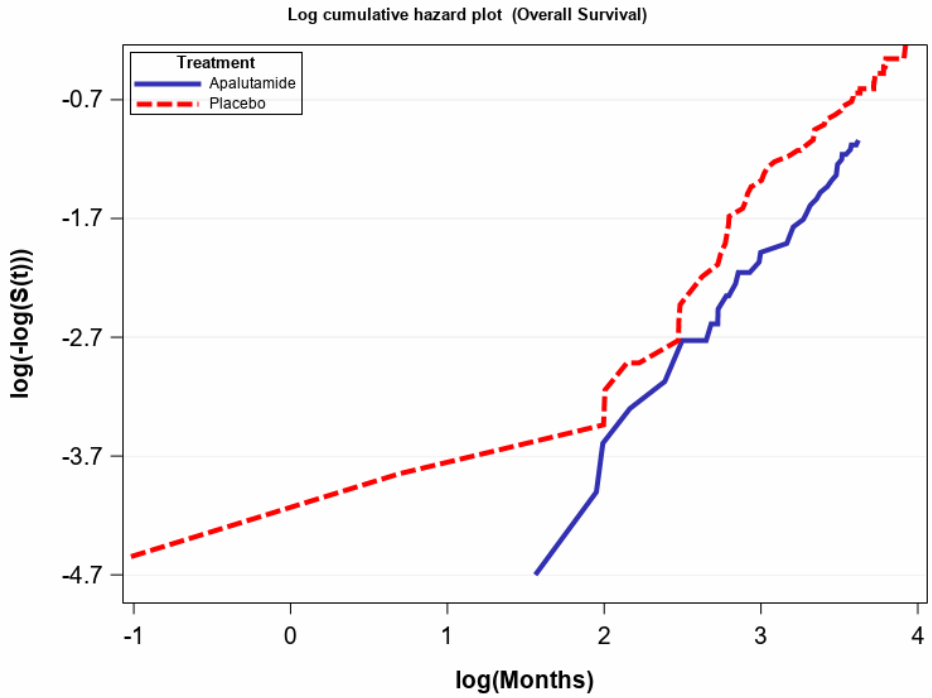
Figure 41. PFS2 extrapolation: apalutamide + ADT & ADT alone (TITAN, over 75 sub-group, unstratified curves)

[redacted]

	AIC	BIC
Weibull	871.7	881.7
Gompertz	876.1	886.1
Log-logistic	870.4	880.5
Log-normal	874	884.1
Gen gamma	872.8	886.2
Exponential	877.6	884.3

Abbreviations: ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS2, second progression-free survival

Figure 42. Log-cumulative hazard plots (TITAN, over 75 sub-group, OS)



Abbreviations: OS, overall survival

Figure 43. OS extrapolation: apalutamide + ADT & ADT alone (TITAN, over 75 sub-group, unstratified curves)

	AIC	BIC
Weibull	847	857.1
Gompertz	851	861.1
Log-logistic	846.4	856.4
Log-normal	851.2	861.3
Gen gamma	848.7	862.1
Exponential	855	861.7

Abbreviations: ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival

Apalutamide for treating prostate cancer [ID1534]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Friday 11 June 2021 email:** NICE DOCS

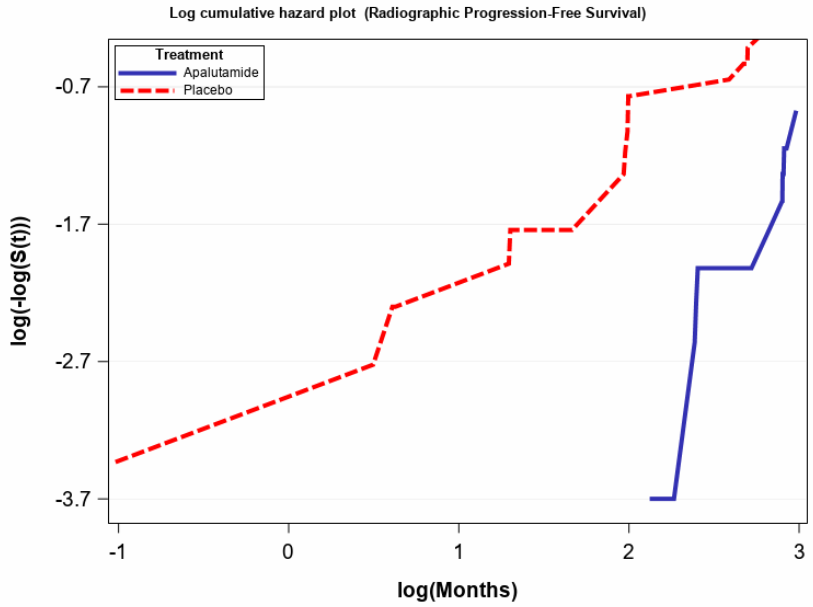
ECOG 1 & over 75 sub-group

Figure 44. TTD extrapolation: apalutamide + ADT (TITAN, ECOG 1 & over 75 sub-group)

	AIC	BIC
Weibull	285.4	289.2
Gompertz	285.6	289.4
Log-logistic	285.7	289.5
Log-normal	290.1	293.9
Gen gamma	287.4	293.1
Exponential	283.9	285.8

Abbreviations: ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; ECOG, Eastern Co-operative Oncology Group; TTD, time to treatment discontinuation

Figure 45. Log-cumulative hazard plots (TITAN, ECOG 1 & over 75 sub-group, PFS)



Abbreviations: ECOG, Eastern Co-operative Oncology Group; rPFS, radiographic progression-free survival

Figure 46. rPFS extrapolation: apalutamide + ADT (TITAN, ECOG 1 & over 75 sub-group, stratified curves)

[redacted]

	AIC	BIC
Weibull	102.6	106.4
Gompertz	105.4	109.1
Log-logistic	102	105.8
Log-normal	101	104.7
Gen gamma	101.5	107.1
Exponential	109.5	111.4

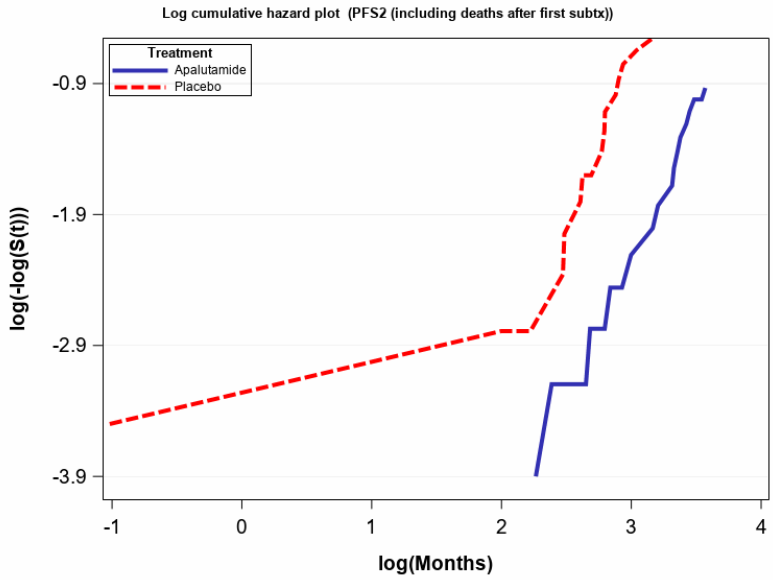
Abbreviations: ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; ECOG, Eastern Co-operative Oncology Group; rPFS, radiographic progression-free survival

Figure 47. rPFS extrapolation: ADT alone (TITAN, ECOG 1 & over 75 sub-group, stratified curves)

	AIC	BIC
Weibull	134.8	137.8
Gompertz	134	137
Log-logistic	134	137
Log-normal	134	137
Gen gamma	136	140.5
Exponential	133	134.4

Abbreviations: ADT, androgen deprivatio therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; ECOG, Eastern Co-operative Oncology Group; rPFS, radiographic progression-free survival

Figure 48. Log-cumulative hazard plots (TITAN, ECOG 1 & over 75 sub-group, PFS2)



Abbreviations: ECOG, Eastern Cooperative PFS2, second progression-free survival

Figure 49. PFS2 extrapolation: apalutamide + ADT & ADT alone (TITAN, ECOG 1 & over 75 sub-group, unstratified curves)

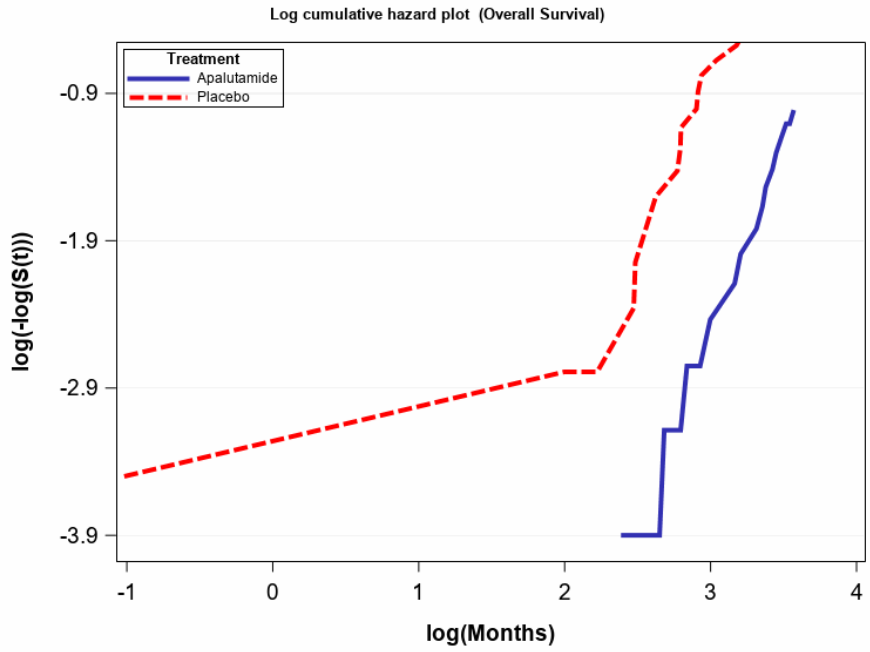
[redacted]

	AIC	BIC

Weibull	352.7	359.9
Gompertz	355	362.2
Log-logistic	350.4	357.6
Log-normal	354.2	361.4
Gen gamma	353.9	363.5
Exponential	354.5	359.3

Abbreviations: ADT, androgen deprivatio therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; ECOG, Eastern Co-operative Oncology Group; PFS2, second progression-free survival

Figure 50. Log-cumulative hazard plots (TITAN, ECOG 1 & over 75 sub-group, OS)



Abbreviations: OS, overall survival

Figure 51. OS extrapolation: apalutamide + ADT & ADT alone (TITAN, ECOG 1 & over 75 sub-group, unstratified curves)

	AIC	BIC
Weibull	344.5	351.8
Gompertz	346.7	353.9
Log-logistic	342.2	349.4
Log-normal	346.1	353.3
Gen gamma	345.7	355.4
Exponential	346.6	351.4

Abbreviations: ADT, androgen deprivation therapy; AIC, Akaike information criterion; BIC, Bayesian information criterion; ECOG, Eastern Co-operative Oncology Group; OS, overall survival

References

1. National Institute for Health and Care Excellence (NICE). Early and locally advanced breast cancer: diagnosis and management - NICE Guideline CG101. 2018.
2. Tombal B. Non-metastatic CRPC and asymptomatic metastatic CRPC: which treatment for which patient? Annals of oncology : official journal of the European Society for Medical Oncology. 2012;23 Suppl 10:x251-8.
3. Schnadig ID, Beer TM. Optimal timing of chemotherapy in androgen independent prostate cancer. Urologic oncology. 2009;27(1):97-100.
4. Smith MR, Cook R, Lee KA, Nelson JB. Disease and host characteristics as predictors of time to first bone metastasis and death in men with progressive castration-resistant nonmetastatic prostate cancer. Cancer. 2011;117(10):2077-85.
5. National Institute for Health and Care Excellence (NICE). TA660: Darolutamide with androgen deprivation therapy for treating hormone-relapsed non-metastatic prostate cancer 2020 [updated 25 November 2020. Available from: https://www.nice.org.uk/guidance/ta660.
6. National Institute for Health and Care Excellence (NICE). FAD: Enzalutamide for treating hormone-sensitive metastatic prostate cancer 2021 [Available from: https://www.nice.org.uk/guidance/gid-ta10488/documents/final-appraisal-determination-document.
7. Mateo J, Fizazi K, Gillessen S, Heidenreich A, Perez-Lopez R, Oyen WJG, et al. Managing Nonmetastatic Castration-resistant Prostate Cancer. Eur Urol. 2019;75(2):285-93.
8. Ng K, Smith S, Shamash J. Metastatic Hormone-Sensitive Prostate Cancer (mHSPC): Advances and Treatment Strategies in the First-Line Setting. Oncology and therapy. 2020;8(2):209-30.
9. Parker C, Castro E, Fizazi K, Heidenreich A, Ost P, Procopio G, et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology. 2020;31(9):1119-34.
10. Lowrance WT, Breau RH, Chou R, Chapin BF, Crispino T, Dreicer R, et al. Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline PART II. The Journal of urology. 2021;205(1):22-9.
11. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guideline®) Prostate Cancer Early Detection. Version 2.2019. 2019.
12. (NPCA) NPCA. Annual Report 2019: Results of the NPCA Prospective Audit in England and Wales for men diagnosed from 1 April 2017 to 31 March 2018 (publshed January 2020). 2020.
13. Janssen. [DoF] Clinical advisory board for apalutamide in the treatment of mHSPC. 2019.
14. National Health Service. Clinical Commissioning Policy Statement: Docetaxel in combination with androgen deprivation therapy for the treatment of hormone naïve metastatic prostate cancer 2016 [Available from: https://www.england.nhs.uk/wp-content/uploads/2016/01/b15psa-docetaxel-policy-statement.pdf.
15. Gravis G, Boher JM, Joly F, Soulie M, Albiges L, Priou F, et al. Androgen Deprivation Therapy (ADT) Plus Docetaxel Versus ADT Alone in Metastatic Non castrate Prostate Cancer: Impact of Metastatic Burden and Long-term Survival Analysis of the Randomized Phase 3 GETUG-AFU15 Trial. Eur Urol. 2016;70(2):256-62.
16. Gravis G, Fizazi K, Joly F, Oudard S, Priou F, Esterni B, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. The Lancet Oncology. 2013;14(2):149-58.
17. Kyriakopoulos CE, Chen YH, Carducci MA, Liu G, Jarrard DF, Hahn NM, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018;36(11):1080-7.
18. Janssen R&D. TITAN Final ANalysis Topline Results. 2020 15 October 2020.
19. Small EJ, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, et al. Apalutamide and overall survival in non-metastatic castration-resistant prostate cancer. Annals of Oncology. 2019.

20. Chi KN, Chowdhury S, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, et al. Apalutamide in Patients With Metastatic Castration-Sensitive Prostate Cancer: Final Survival Analysis of the Randomized, Double-Blind, Phase III TITAN Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2021:Jco2003488.
21. Rathkopf DE, Smith MR, de Bono JS, Logothetis CJ, Shore ND, de Souza P, et al. Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). Eur Urol. 2014;66(5):815-25.
22. Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PF, Sternberg CN, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. The Lancet Oncology. 2015;16(2):152-60.

NICE National Institute for Health and Care Excellence

Apalutamide for treating prostate cancer [ID1534]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Friday 11 June 2021 email:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Prostate Cancer UK**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
Name of commentator person completing form:	[redacted]

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Apalutamide for treating prostate cancer [ID1534]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Friday 11 June 2021 email:** NICE DOCS

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The committee's recommendation risks leaving an unmet need for men who have progressed to metastatic disease from localised/locally advanced disease. If apalutamide cannot be approved for the whole population, it must be considered for this subgroup with ADT as the comparator, using evidence of clinical benefit from the unsuitable for chemotherapy population. The necessity of approving a Novel Hormonal Agent (NHA) for patients with hormone-sensitive metastatic prostate cancer has recently been with respect to those patients who are unsuitable for docetaxel chemotherapy. These patients lose out on additional months of life that chemotherapy provides, are treated with Androgen Deprivation Therapy (ADT) and could benefit from an NHA. This is because NHAs in this indication provide a similar life extension to docetaxel. The recent approval of enzalutamide in this indication is, for most of these patients, an excellent solution. However, there is still a potential for an unmet need. This depends on whether the enzalutamide approval includes patients who have progressed to hormone-sensitive metastatic prostate cancer from localised/locally advanced disease. The marketing authorisation appears to include them, and we would welcome confirmation of their eligibility for enzalutamide. If, however, the approval of enzalutamide does not include this progressed population then apalutamide can deliver to an unmet need in this patient sub-group, as we know that these patients are included in the marketing authorisation. These patients, unless high-risk locally advanced, are not indicated for docetaxel and are most likely to only receive ADT until they progress to hormone-refractory disease. The docetaxel arm of the STAMPEDE trial showed benefit in patients with newly diagnosed metastatic and high-risk locally advanced prostate cancer (this population was defined as having at least two of: T category T3/4, PSA≥40ng/ml or Gleason sum score 8-10 as well as intention to treat with radical radiotherapy (unless there is a contra-indication). The benefit in the population who had progressed from localised/locally advanced disease was unclear because of the small size of this subgroup, resulting in large confidence intervals (HR 0.8, CI 0.26 –2.48). Prior exposure to ADT for a duration of >12 months, or any prior exposure completed less than 12 months before randomisation, were exclusion criteria for the trial. This is likely to exclude patients diagnosed with localised and locally advanced prostate cancer, who are often treated with ADT. We hear anecdotally that some of these patients are prescribed docetaxel on an off-label basis anyway, but this is without any evidential backing. There is limited evidence to show whether docetaxel is clinically effective at this stage of the disease in contrast to the benefit shown for apalutamide in patients unsuitable for chemotherapy. Fundamentally, the most positive outcome from this appraisal would be approval of apalutamide for the whole population, for which it must demonstrate cost-effectiveness against docetaxel. If it is not able to achieve this, it is imperative that evidence of the benefit of apalutamide in the chemotherapy unsuitable population is used to make it available to patients that have progressed to hormone-sensitive metastatic prostate cancer from localised/locally advanced disease. The comparator for this group must be ADT.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Apalutamide for treating prostate cancer [ID1534]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Friday 11 June 2021 email:** NICE DOCS

2	Apalutamide provides an opportunity to approve a life-extending treatment for patients who cannot tolerate enzalutamide, as highlighted by provision during COVID. There is still a sub-population that is not served by the approval of enzalutamide. During the COVID pandemic, NHS England has been providing enzalutamide and abiraterone to patients with newly-diagnosed metastatic prostate cancer in lieu of docetaxel chemotherapy. This has been done to mitigate the COVID-associated risks of attending hospital to receive chemo and of potential immune suppression. The terms of this provision state that enzalutamide should be the first choice, with abiraterone being made available to those who cannot tolerate enzalutamide. SACT data indicates that approximately 270 patients per month have been prescribed enzalutamide through this interim provision during the pandemic, while around 22 per month have been prescribed abiraterone. This suggests that a little under 10% of new metastatic hormone-sensitive prostate cancer patients fall into the group who cannot tolerate enzalutamide. Some of these patients will also be chemotherapy-unsuitable, and for these patients the continuation of an alternative treatment will deliver to an unmet need. Apalutamide provides the opportunity to address this unmet need for patients who are unsuitable for enzalutamide, such as patients with a history of, or predisposing factors to seize or seizure disorders, with the appropriate comparator being ADT.
3	We are concerned by the committee's consideration of innovation. In the non-metastatic hormone-relapsed indication, darolutamide was not used as a comparator because it had not been approved when this treatment was submitted for appraisal, yet in section 3.42 on innovation darolutamide availability is used as the sole reason to deny innovation in apalutamide. This is inconsistent. The committee should treat the submission of the treatment as a "freeze in time" and base all decisions on provision at that time. Similarly, in the hormone-sensitive metastatic indication, the committee has said apalutamide "may be" innovative pending the outcome of other ongoing appraisals. Again, this has no logical basis – the treatment is either innovative or it is not, and this should be determined based on the circumstances at the time it was submitted to NICE. Innovation cannot be determined retroactively based on other results – it is entirely possible that two companies could be independently developing innovative treatments for the same indication and their appraisals should not affect one-another.
4	Using a reduced measure of the effectiveness of apalutamide for a chemotherapy-unsuitable population, due to presuming these patients are old and frail, is not justified. A broader range of patients is included in this group. Section 3.40 states that "[the committee] considered that it would be unlikely to make age-based recommendations". We agree that an age cut-off alone would not be a suitable solution, but this does not preclude the committee from approving apalutamide for a chemo-unsuitable population. Significant work over the course of the appraisal of abiraterone has gone into determining the nature of this population and expressing it independently of age, identifying several criteria that make patients unsuitable for chemotherapy including peripheral neuropathy and poor performance status. This means there is no necessity to make an "age-based recommendation". Indeed, this population is not solely comprised of those older and frailer patients, or patients with significant comorbidities, who may not tolerate the harmful side-effects of docetaxel. It also includes patients who have progressed to metastatic prostate cancer from localised / locally advanced disease. As discussed above (Point 1), there is no evidence for the effectiveness of docetaxel in this population. Chemotherapy is therefore not a suitable treatment for them, and makes them part of the chemo-unsuitable population. These patients would not be expected to be primarily old and frail, but will likely be a cross-section of all prostate cancer patients. The "chemotherapy-unsuitable" group is therefore much wider than a proxy for "older patients". There is no reason to assume worse treatment effectiveness among this group, even if hazard ratios are slightly worse in older subgroups of trial populations (though the wide confidence intervals for older subgroups are usually a result of low patient numbers).

Apalutamide for treating prostate cancer [ID1534]

Consultation on the appraisal consultation document – deadline for comments 5pm on **Friday 11 June 2021 email:** NICE DOCS

	Having thus demonstrated that the "chemotherapy-unsuitable" population also includes patients whose unsuitability is the result of disease progression to metastatic prostate cancer, the committee should accept the effectiveness of apalutamide from whole-population figures within the trial rather than an older-age subgroup of trial participants when considering this group.
5	
6	
7	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	
Other role	
Organisation	British Uro-oncology Group (BUG)
Location	
Conflict	
Notes	Our comments express our huge disappointment on this ACD which is not recommending the option of apalutamide for prostate cancer patients.

Comments on the ACD:

The NICE ACD not recommending Apalutamide for treatment of metastatic hormone sensitive prostate cancer (MHSPC) and non-metastatic castration resistant prostate cancer (NMCRPC) is disappointing and deprives patients in this setting the advances made to improve their outcomes from prostate cancer including improving survival.

In MHSPC setting the current options through NICE guidelines are limited to ADT alone or ADT+Docetaxel. The Covid guidelines for CDF enabled the use of Enzalutamide in this setting through the CDF.

The international guidelines (EAU, NCCN) recommend the option of ADT+Abiraterone and Prednisolone or ADT+ Enzalutamide or ADT+Apalutamide as strong recommendations in MHSPC setting.

Whilst ADT+Docetaxel is also a strong recommendation in MHSPC setting, however, the National Prostate Cancer Audit (NPCA) reported that even in the pre-covid era the uptake of upfront Docetaxel was 26%. This implies that there are a vast majority of cases in the MHSPC setting who either do not want to have chemotherapy or are unsuitable for chemotherapy.

It is vitally important that the MHSPC population has the option of ADT+ARTA (Androgen Receptor Targeted Agent). Therefore, it would be our sincere request that the option of ADT+Apalutamide is approved in this setting. Otherwise, the outcomes for prostate cancer patients in this setting are very likely to suffer in contrast to the countries where it would be standard practice to offer ADT+ARTA.

In NMCRPC setting, whilst the approval of Darolutamide has been a very important aspect, the option of apalutamide would have enabled choice. The data of the SPARTAN trial with Apalutamide in NMCRPC setting has a longer follow-up than the data of Darolutamide in the ARAMIS trial and therefore, clinicians and patients would welcome the choice of proven agents in this setting. This would not be any different to the several TKI options in the first line setting in advanced renal carcinoma which are NICE approved. The aspect regardingsome of the assumptions in the economic modelling being uncertain would apply similarly to the assessment for Darolutamide with ARAMIS trial in NMCRPC setting as it would for Apalutamide with SPARTAN trial in NMCRPC setting. If anything, the follow-up of the SPARTAN trial is significantly longer than the ARAMIS trial and therefore likely to reduce the uncertainties in the economic modelling.

In the section ‘Why the committee made these recommendations’ (Page 3 of 41) it states that ‘Clinical trial evidence suggests that, compared with placebo plus ADT, apalutamide plus ADT increases the time until the disease progresses and how long people live. But this evidence is uncertain because in the trials some people could switch from placebo plus ADT to apalutamide plus ADT. Also, some people could have treatments not available in the NHS.’ The trial allowed for crossover after the interim analysis and despite the crossover the significant statistical benefit

for overall survival was maintained and the HR for OS was 0.65 (HR for OS at interim analysis was 0.67). Therefore, it is difficult to understand the committee's statement that the switch made the evidence uncertain.
The British Uro-Oncology Group would request the committee to review the evidence and also consider that the inability to offer these patients a novel Androgen Receptor Targeted therapy which improves overall survival would be significantly detrimental to the prostate cancer treatment outcomes in the country.

CONFIDENTIAL UNTIL PUBLISHED

Evidence Review Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Apalutamide for treating prostate cancer

Evidence Review Group's critique of the company's response to the appraisal consultation document (June 2021)

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	Keith Cooper, Senior Research Fellow, Health Economics. Irina Tikhonova, Senior Research Fellow in Health Technology Assessment & Modelling. Inês Souto Ribeiro, Senior Research Assistant, Health Economics. Jonathan Shepherd, Principal Research Fellow, Evidence Synthesis.
Correspondence to	Dr Jonathan Shepherd Southampton Health Technology Assessments Centre (SHTAC) Wessex Institute Alpha House Enterprise Road, University of Southampton Science Park Southampton SO16 7NS www.southampton.ac.uk/shtac
Date completed	25th June 2021

Contents

List of tables

[redacted]

1. Introduction

This document is the Evidence Review Group's (ERG) summary and critique of the response by the company, Janssen-Cilag Ltd, to the NICE appraisal consultation document (ACD) (Issue date: May 2021) for this technology appraisal [ID1534]. The ERG received the company's response on 14th June 2021.

The company's ACD response form contains the following information:

- A written response to selected committee comments made at the first appraisal committee meeting discussion of this topic on 4th March 2021.
- A set of updated cost-effectiveness results for both the metastatic hormone sensitive prostate cancer (mHSPC) and the non-metastatic hormone relapsed prostate cancer (nmHRPC) indications, incorporating:
    - An updated confidential Patient Access Scheme (PAS) price discount for apalutamide (subject to necessary approval).
    - A revised company base case incorporating the committee's preferred assumptions
    - Scenario analyses to address the appraisal committee's comments
- An updated version of the company's economic model accompanies the response form.

In this report we present a brief critique of the company's response to each of the five issues in the company's ACD response form, namely:

- Population who do not currently receive docetaxel
- Model face validity
- Adjusting for cross-over and second androgen receptor inhibitor
- The use of flexible modelling
- Modelled cost of apalutamide

We also provide a validation of the results of the company's updated cost-effectiveness analysis.

2. Population who do not currently receive docetaxel

In order to further explore the cost-effectiveness of apalutamide plus ADT in mHSPC patients who do not currently receive treatment with docetaxel, the company present selected subgroup data from the TITAN trial to inform a cost effectiveness scenario analysis (Table 8 of the company ACD response).

The company proposes five main subgroups of patients (based on subgroups in the TITAN trial) who do not currently receive docetaxel, for whom apalutamide plus ADT could be a potential treatment option (as shown in Table 1 below).

Table 1 Company's proposed subgroups of mHSPC patients who do not currently receive docetaxel

Subgroup not currently receiving docetaxel	Justification	Docetaxel status[a]
Metastasis stage at diagnosis of M0 (non-metastatic).[b]	M0 patients do not meet the NHS England docetaxel commissioning policy requirement to "have newly diagnosed, metastatic, prostate cancer"	Ineligible
Low volume disease	Docetaxel is not as effective in low volume disease and is therefore not routinely offered to patients with this characteristic	Ineligible
Patients with a baseline ECOG score of 1	Three "proxy sub-groups" selected by the company to represent patients with poor fitness and/ or co-morbidity that would make them unsuitable to tolerate docetaxel.	Unsuitable
Patients over the age of 75		
Patients with a baseline ECOG score of 1 who are over 75 years old	Clinical prognostic factors which do not meet NHS England docetaxel commissioning policy inclusion criteria	Ineligible

[a] This is an overall classification of the reason why patients do not receive docetaxel. The ERG has applied 'ineligible' or 'unsuitable' based on our interpretation of the company's information.

[b] This appears to be the same subgroup referred to as 'locally advanced sub-group' in the Appendix to the company's response document.

The company acknowledge that none of these sub-groups accurately reflects the group of patients who are unsuitable for treatment with chemotherapy. The ERG notes that there has been extensive discussion within this appraisal (e.g. at technical engagement), and in related prostate cancer NICE appraisals, about the defining characteristics of a subpopulation of prostate cancer patients who are ineligible or unsuitable to receive docetaxel. In these discussions age and performance status were proposed as key

indicators of suitability to take docetaxel. We do not have any further comments to the appropriateness of the company's chosen subgroups, but further expert clinical opinion may be useful to confirm clinical appropriateness.

The ERG has the following comments on the company's scenario analysis (Table 8 of the company's ACD response) in patients who do not currently receive docetaxel:

- The data informing this analysis is from the final analysis of the TITAN trial (cut off date September 2020) and is therefore up to date. The company submitted these data at technical engagement, thus these have already been examined by the ERG and been presented to the appraisal committee.
- In the appendix to the response to ACD the company provide survival extrapolations, and model fit statistics, for each of the subgroups for the following outcomes: TTD; rPFS; PFS; PFS2 and OS. The ERG has not checked the curves in detail for fit and clinical plausibility.
- We note, however, that the OS estimates used in the model for these subgroup analyses are the same as those used for the whole TITAN trial population. We would have expected the sub-group specific OS estimates to be used.
- We reiterate our previously expressed caveats about uncertainties in trial subgroup analyses, including low numbers of patients in some subgroups and lack of sufficient statistical power.

3. Model face validity

The company comments that overall survival estimates presented at the NICE committee meeting for apalutamide on 4th March 2021 on slides 29 and 68 were incorrect. They present the correct post-progression estimates. The ERG confirms the pre- and post-survival estimates presented by the company in the ACD response Table 2.

The committee requested a scenario with equal post-progression survival for both treatment arms. The company completed this scenario (section 7) which we have checked and verified in the model. We consider the approach taken to conduct this scenario is reasonable and appropriate.

4. Adjusting for cross-over and second androgen receptor inhibitor

The use of unadjusted PFS2 in the COU-AA-302 trial

The active treatment in COU-AA-302 (abiraterone acetate plus prednisone) had a considerably bigger impact on PFS2 in that trial when compared to OS: the respective HRs were [redacted] and [redacted] (see CS Appendix R.2). In our critique of the company's TE response we argued that adjusting PFS for cross-over in COU-AA-302 would have a more pronounced effect on the adjusted HRs in SPARTAN and TITAN, and would likely increase the cost-effectiveness estimates.

We note that the sources the company referred to (Rathkopf et al. 2014 [1] and Ryan et al. 2015[2]) in support of their statement that PFS in COU-AA-302 was not impacted by cross-over, do not report on the impact of cross-over on PFS.

According to Ryan et al. 2015, at the interim analysis 2 of the COU-AA-302 trial data conducted in December 2011, the independent data monitoring committee (IDMC) recommended unblinding the study and allowing cross-over from the placebo arm to active therapy, and a substantial proportion of patients, 17% (93 out of 542) initially enrolled in the placebo arm went on to receive abiraterone. Therefore, there is no reason to believe that the PFS in this study was not affected by treatment cross-over.

5. The use of flexible modelling

The committee expressed a request to see the fitting of additional survival curves to model certain survival endpoints. The company did not provide any further analyses in response to this request, citing their extensive clinical consultation in support of their original approach. They also state that the fact that there was no indication of a distinct change in hazards over time in the survival curves as justification for not using flexible modelling (with reference to NICE DSU Technical Support Document 21). However, the ERG would like to reiterate that our original suggestion (in the ERG report) to consider flexible modelling was because, in our view, the parametric survival curves did not provide a close enough fit for the long-term estimates of metastatic free survival. It would be informative to see alternative scenarios using flexible modelling that is more closely fitted to the ERG's clinical experts' opinion.

6. Modelled cost of apalutamide

The committee have indicated that the cost of treatment with apalutamide was artificially capped and therefore the treatment cost may have been underestimated.

The ERG considers that it is appropriate for the company to cap the costs of treatment by assuming that there are not more patients on treatment than who remain progression-free. Further, we do not consider this assumption will lead to an underestimation of the cost of apalutamide in the model.

7. Revised company base case

The ERG has checked and verified the results submitted by the company. We have also replicated the results using the current PAS discounts for all the treatments in a confidential appendix.

References

1. Rathkopf DE, Smith MR, de Bono JS, et al. Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). *European urology* 2014;66(5):815-25. doi: 10.1016/j.eururo.2014.02.056 [published Online First: 2014/03/22]
2. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol* 2015;16(2):152-60. doi: 10.1016/s1470-2045(14)71205-7 [published Online First: 2015/01/21]