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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Apalutamide for treating prostate cancer [ID1534]

Appraisal Committee Meeting – 4 March 2021
1st Committee meeting

The following documents are made available to the Company and experts:

The **final scope and final stakeholder list** are available on the NICE website.

Pre-technical engagement documents

1. **Company submission summary** from Janssen

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Prostate Cancer UK
   b. Tackle Prostate Cancer

4. **Evidence Review Group report** prepared by Southampton Health Technology Assessment Centre

5. **Evidence Review Group report – factual accuracy check**

Post-technical engagement documents

6. **Technical engagement response from company**

7. **Technical engagement responses from experts:**
   a. Professor Amit Bahl, Consultant Clinical Oncologist – clinical expert, nominated by Janssen
   b. Dr Stephen Allen, Patient Representative – patient expert, nominated by Tackle Prostate Cancer
   c. Miss Rebecca Leszczynski, Senior Knowledge Officer – patient expert, nominated by Prostate Cancer UK

8. **Technical engagement responses from consultees and commentators:**
   a. Bayer

9. **Evidence Review Group critique of company response to technical engagement** prepared by Southampton Health Technology Assessment Centre

Appraisal Committee Meeting presentation slides *– to follow*

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Please note that the full submission, appendices to the company's submission and company model will be available as a separate file on NICE Docs for information only.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Apalutamide for treating non-metastatic hormone-relapsed prostate cancer and metastatic hormone-sensitive prostate cancer [ID1534]

Document A

Company evidence submission summary for committee

July 2020

Janssen-Cilag Ltd. confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

File name	Version	Contains confidential information	Date
ID1534_Apalutamide nmHRPC and	FINAL	Yes	16th July 2020

mHSPC_Form A_FINAL_160720 [ACIC]			

Instructions for companies

This is the template you should use to summarise your evidence submission to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. This document will provide the appraisal committee with an overview of the important aspects of your submission for decision-making.

This submission summary must not be longer than 25 pages, excluding the pages covered by this template. If it is too long it will not be accepted. Please submit a draft summary with your main evidence submission. The NICE technical team may request changes later.

When cross referring to evidence in the main submission or appendices, please use the following format: Document, heading, subheading (page X).

For all figures and tables in this summary that have been replicated, cross refer to the evidence from the main submission or appendices in the caption in the following format: Table/figure name – document, heading, subheading (page X).

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

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Submission summary

A.1 Background

Apalutamide is licensed for the treatment of patients with prostate cancer in two places in the treatment paradigm. In January 2019, the European Medicines Agency granted apalutamide a marketing authorisation for the treatment of adults with non-metastatic hormone-relapsed prostate cancer (nmHRPC) at high risk of developing metastatic disease.[1] This was followed by a second marketing authorisation in January 2020, for adults with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT).[2] Following delay to the submission for nmHRPC (pending additional trial data), a combined submission was agreed with NICE to allow comprehensive assessment of the value of the molecule across the prostate cancer pathway. The benefits of a combined submission being that more mature data from nmHRPC can be used to contextualise the (currently) less mature data for mHSPC. As such, this submission presents the clinical and cost effectiveness of apalutamide in both indications, compared with respective standards of care in the treatment pathway.

Patients with high-risk nmHRPC and with mHSPC represent acute cohorts with unmet need in the prostate cancer pathway. Despite being broadly asymptomatic or mildly symptomatic at diagnosis, disease progression to metastatic hormone-relapsed prostate cancer (mHRPC) is inevitable and occurs between 14.7 and 16.2 months in high-risk nmHRPC [3, 4] and within 20.2 to 22.1 months in mHSPC[5, 6] for patients receiving ADT alone. Indeed, the common goal of treatment for nmHRPC (high-risk) and mHSPC is to delay the development of mHRPC, a disease state associated with significant deterioration in health-related quality of life (HRQL), psychological burden, greater resource use, increased healthcare costs and significantly poorer prognosis.[7-9 10, 11]

Apalutamide represents an important advancement in the treatment paradigm for patients with prostate cancer. An extensive and robust clinical evidence base supports the substantial value apalutamide offers patients, their carers, clinicians and the NHS. Compared with ADT alone, the current standard of care, apalutamide plus ADT has demonstrated a statistically significant overall survival (OS) benefit in patients with high-risk nmHRPC and with mHSPC.[6, 12] Apalutamide not only improves survival, it also delays disease progression (and the associated symptomatic sequelae), delays the need for cytotoxic chemotherapy and increases time spent with a good quality of life, compared with standard of care.[4, 6]

Apalutamide reduces patient anxiety over rising prostate-specific antigen (PSA) levels with an immediate, meaningful and durable impact on PSA levels.[13] Moreover, the time from randomisation to disease progression on first subsequent therapy, or death (PFS2), is significantly extended with apalutamide. This demonstrates that early use leads to better long-term outcomes versus waiting to use a novel therapy in

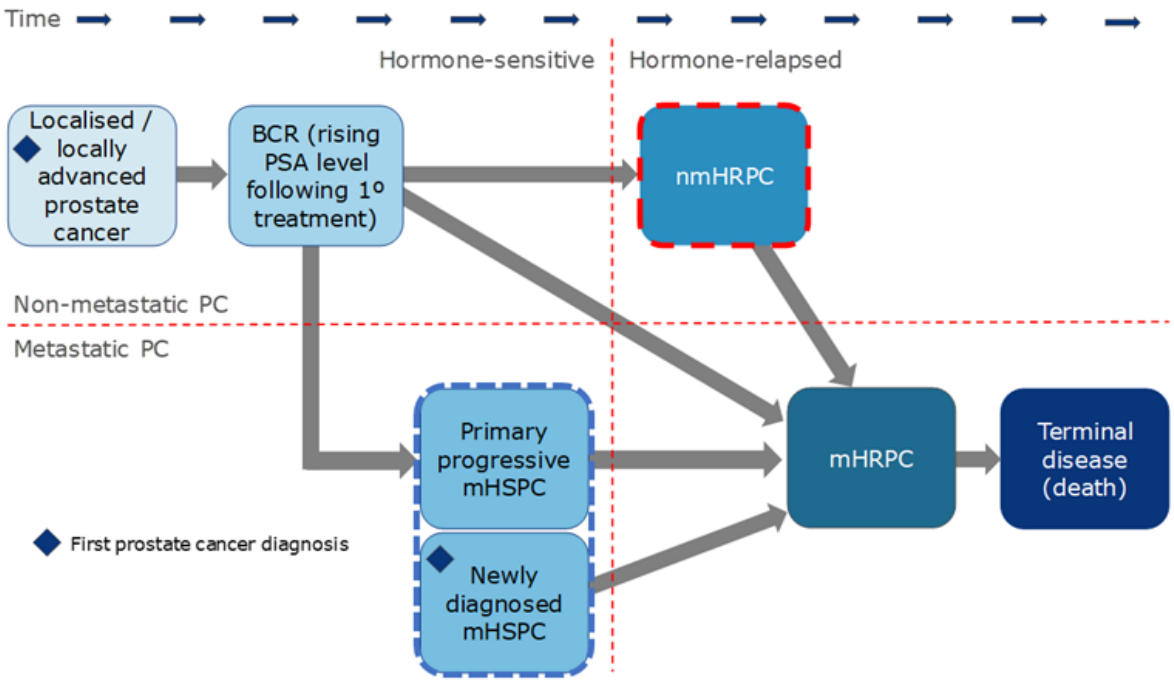
mHRPC.[6, 14] Furthermore, apalutamide has the potential to simplify disease management; it is an oral tablet taken once a day in the comfort of a patient's home, with no added hospital visits, mandated monitoring or concomitant corticosteroids.[15, 16]

A.2 Health condition

Prostate cancer is now the most diagnosed cancer type in England, having overtaken breast cancer in 2018.[17] Between 2016 and 2017, there were 41,201 new cases of prostate cancer in England; of these, 84% of patients had non-metastatic disease at diagnosis (meaning the cancer had not spread beyond the pelvis).[17-19] Patients diagnosed with prostate cancer are often in their seventies, and their symptoms are largely determined by the extent of underlying disease; these may range from urinary problems, to tiredness, unexpected weight loss and even bone pain with later-stage disease.[18, 20 21]

An overview of the prostate cancer patient pathway is presented in Figure 1. Apalutamide is licensed for the treatment of patients with high-risk nmHRPC and with mHSPC, as highlighted respectively by the red and blue dashed borders.

Figure 1: PC disease progression



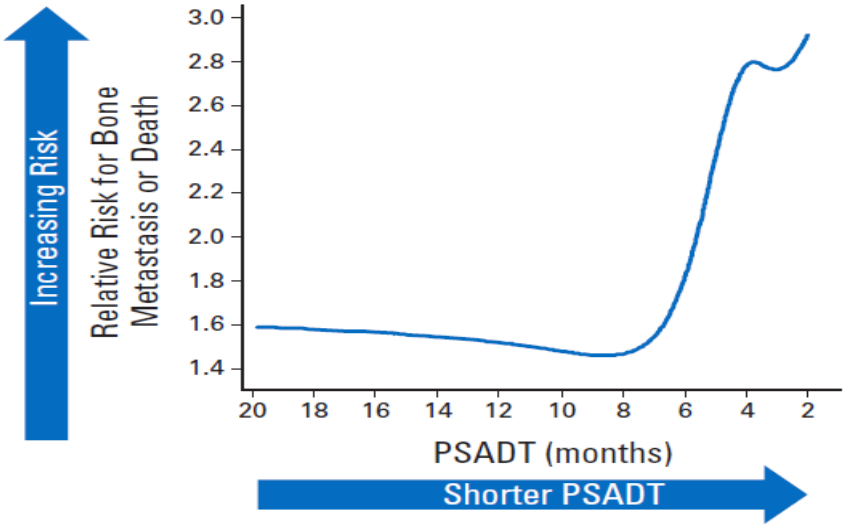
Abbreviations: BCR: biochemical recurrence; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; nmHRPC: non-metastatic hormone-relapsed prostate cancer; PC: prostate cancer; PSA: prostate-specific antigen.
Notes: blue dashed borders depict the mHSPC patient group and the red dashed borders depict the nmHRPC patient group of interest to this submission.

A.2.1 High-risk nmHRPC

In the non-metastatic disease setting, a small population of men can be described as having high-risk nmHRPC. High-risk nmHRPC is characterised by rising PSA levels (i.e. biochemical recurrence) while on ADT, no evidence of distant metastases (with conventional imaging) and a PSA doubling time (PSADT) of ≤ 10 months.[22, 23] The relationship between PSADT and the risk for bone metastasis or death in men with nmHRPC is illustrated in Figure 2.

Patients with high-risk nmHRPC have developed resistance to hormone therapy but are yet to develop distant metastases based on conventional imaging techniques (CT and bone scans). They are typically asymptomatic or mildly symptomatic, and predominantly present initially with urinary problems. [13] As a result, patients often have HRQL comparable to that of healthy individuals, which may significantly downplay the severity of this disease.[13]

Figure 2: Relationship between PSADT and the risk for bone metastasis or death in men with nmHRPC



Abbreviations: nmHRPC: non-metastatic hormone-relapsed prostate cancer; PSADT: prostate-specific antigen doubling time.
Source: Smith et al. (2013).[23]

For these patients, primary therapy with curative intent has failed, as they have subsequently experienced rising PSA levels, indicating persistent cancer activity, called biochemical recurrence.[24] Despite having received hormone therapy for 1 to 2 years, these patients have developed resistance to ADT and have no alternative treatment option that can delay further progression.[24, 25]

In the UK there are estimated to be 1,769 patients diagnosed with high-risk nmHRPC each year whose condition remain insufficiently managed on ADT alone. See Appendix M for patient number calculations.

A.2.2 mHSPC

Patients with mHSPC have either not previously received hormone therapy or are continuing to respond to hormone therapy (i.e. are yet to develop mHRPC).[26] These patients have metastatic disease, meaning that their cancer has spread to more distant parts of the body such as the bone, non-regional lymph nodes, viscera (e.g. lung, liver) and the brain. Metastases are the primary source of morbidity and mortality in patients with prostate cancer.[27-29]

Patients with mHSPC may be identified at initial diagnosis, or after progression to mHSPC from localised disease.[30] In approximately 16% of all new cases of prostate cancer, disease has already spread to distant parts of the body[19], and a further 25% of patients with localised disease will likely progress to mHSPC.[31]

The extent of symptomatic disease varies for patients diagnosed with mHSPC. Patients may experience a range of urinary problems, fatigue, bone pain (attributed to bone metastases), numbness and weakness, all of which can lead to further complications such as skeletal-related events and urethral obstruction if left insufficiently managed.[8-10, 30]

Most patients with mHSPC in the UK are still only treated with standard hormone therapy (i.e. ADT), a level of care that has remained unchanged for decades despite advancements in novel anti-cancer therapies.[30] ADT alone is poor at delaying disease progression, ineffective at delaying the deterioration of HRQL and unable to prolong survival,[32] the majority of patients develop resistance within 1 to 2 years as mHRPC develops.[33]

For patients with more extensive or aggressive metastatic disease at diagnosis, docetaxel chemotherapy is considered in addition to ADT; however, only 27% of patients in the UK currently receive docetaxel at diagnosis since, due to tolerability concerns, they must be fit enough and willing to receive it.[19] Patients who have not yet developed mHRPC still have a good quality of life and therefore have a desire to delay or avoid treatment with chemotherapy. The proportion of patients receiving docetaxel plus ADT has been drastically reduced in the current environment of coronavirus disease (COVID-19) in an effort to curtail the number of hospital visits necessary for the administration of chemotherapy and due to the risk of neutropenia.[34]

In the UK, there are estimated to be 9,629 patients diagnosed with mHSPC each year and the majority remain insufficiently managed on ADT alone. See Appendix M for patient number calculations.

A.2.3 Unmet need

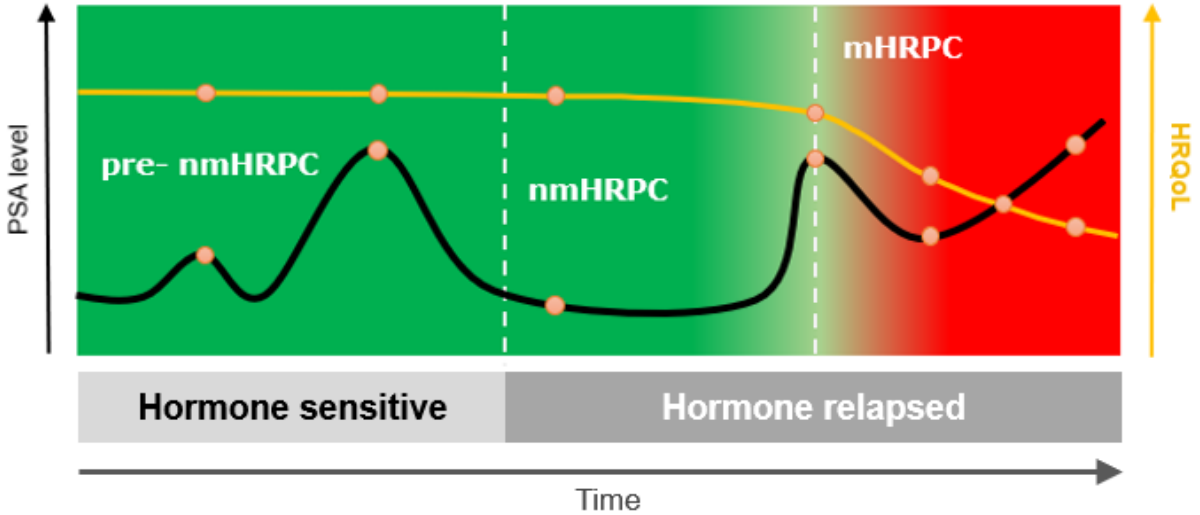
On standard hormone therapy, nmHRPC (high-risk) and mHSPC patients progress to mHRPC in between 14.7 and 16.2 months, and between 20.2 and 22.1 months,

respectively.[3, 4,5, 6] The consequential psychological burden of inevitable progression to mHRPC is understandably high.[35] Furthermore, median OS on ADT alone is 56.3 to 59.9 months for nmHRPC.[14, 36] and 34.7 to 54.2 months for mHSPC patients.[5, 37-39]

Patients with high-risk nmHRPC and patients with mHSPC (who are not fit enough or willing to receive docetaxel) represent an area of high unmet need. Currently, their only option is to remain sub-optimally treated with ADT alone until the inevitable progression to mHRPC, at which point alternative anti-cancer therapies are available.[20] Docetaxel is associated with substantial tolerability concerns and even in patients fit enough and willing to receive docetaxel there is a substantial impact on quality of life.[40-42] A novel treatment is needed that demonstrates efficacy in all patients with mHSPC, irrespective of disease volume, risk stratification, nature of initial diagnosis or prior treatment history.

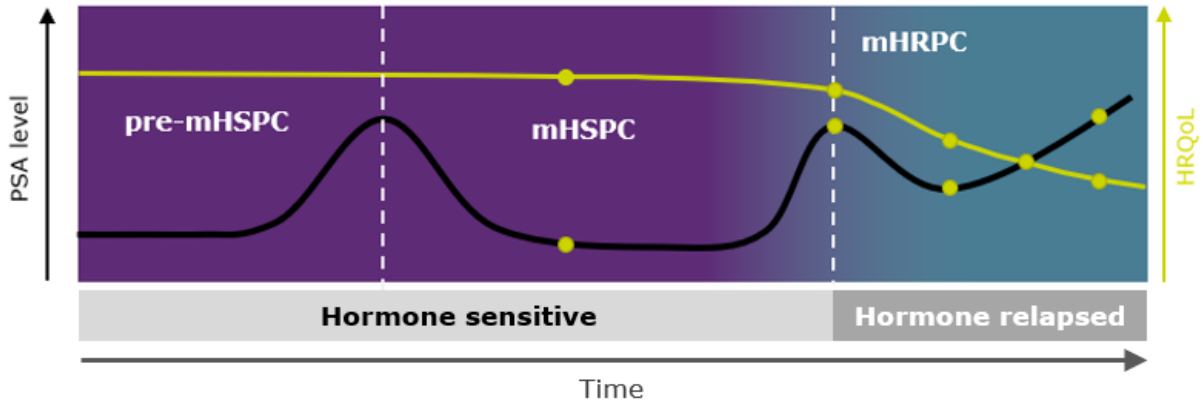
Analogous to breast cancer, where novel treatments are initiated early to prevent recurrence or progression to metastatic disease for patients at high risk of disease progression[43], the main goal when treating patients with high-risk nmHRPC and with mHSPC is to delay the development of mHRPC, because this disease state is associated with debilitating symptoms (haematuria, worsened fatigue and extensive bone pain), impaired HRQL, greater resource use and healthcare costs, and poorer prognosis.[44-46] Figure 3 and Figure 4 visualise how progression to mHRPC is associated with reductions in HRQL and changing PSA levels.

Figure 3: Representation of decline in HRQL with prostate cancer disease progression in patients presenting with non-metastatic prostate cancer



Abbreviations: HRQL: health-related quality of life; mHRPC: metastatic hormone-relapsed prostate cancer; nmHRPC: non-metastatic hormone-relapsed prostate cancer; PSA: prostate-specific antigen.

Figure 4: Representation of decline in HRQL with prostate cancer disease progression in patients presenting with mHSPC



Abbreviations: HRQL: health-related quality of life; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; PSA: prostate-specific antigen.

A.2.4 Patient experiences

Given the disparity in treatment attributes between novel hormone therapy and existing standard of care, patient preferences are an important consideration in the management of nmHRPC (high-risk) and mHSPC. Three exercises were conducted to understand patient preferences and the psychological and emotional impact of the disease and treatment on UK patients:

- A patient workshop to understand the experiences and treatment preferences of HRPC patients
- In-depth qualitative interviews carried out with 11 men living with metastatic prostate cancer
- Group discussion involving seven prostate cancer nurses from across England and Wales to understand the needs of patients with prostate cancer

The methods for all three exercises are presented in Appendix N

Findings from this research indicate that for men living with prostate cancer, by far the biggest non-physiological impact of the disease is emotional and physical emasculation: a loss of sense of personal identity and the ability to provide for their family. Patients lived with constant anxiety and fear of progression, worried about every symptom and were obsessed with worsening PSA levels.[47] This is supported by the findings of previous studies;[7, 48] progression to mHRPC and the development of severe symptoms negatively affect patients' lives emotionally, physically and socially.[7, 48]

One patient in the patient workshop described how his depression had become so severe that he had contemplated suicide. This impact of prostate cancer on mental health is supported by published results from a national retrospective cohort study that investigated 328,372 patients with urological cancers (bladder, kidney and

prostate). The study showed that these patients are five times more likely than the general population, and 63% more likely than other cancer patients to commit suicide.[49]

With regard to treatment, all men interviewed wished for alternative treatment options that preserve length of life without impacting quality of life (these two properties were viewed as mutually exclusive). Indeed, many nmHRPC patients indicated that they would have taken medication to delay metastasis if this had been available, even if they were asymptomatic.[35] Patients also placed substantial value on avoiding the development of metastases and treatment with chemotherapy.[50] Indeed, nurses highlighted that the main concern for men living with high-risk nmHRPC was the lack of active treatment as well as a lack of a well-defined treatment approach. This leads to uncertainty and leaves them feeling like a ticking time bomb, waiting to become metastatic without any intervention.[51]

Moreover, while hormone therapy (ADT) is viewed as causing a continued loss of masculinity, chemotherapy was associated with fear due to sickness and loss of hair (making it impossible to hide from others or themselves that they have cancer). Hospital attendance was found to carry a huge burden for all men living with prostate cancer as it impacted their time, travel was costly, and it reinforced a sense of being sick.[47]

Attitudes about disease progression to mHRPC differed depending on disease stage. Men with mHSPC placed more value on length of life; for example, time with family, and were more likely to accept any treatment that prolonged life, even if quality of life was compromised. For those men who were interviewed, as the disease progressed, some came to terms with death as treatment options ran out, and priorities shifted to comfort and dignity. These patients became less willing to try a treatment that risks side effects and wanted remaining time to be as comfortable as possible.[47]

A.2.5 Concluding remarks

In summary, patients with high-risk nmHRPC or mHSPC will inevitably progress to mHRPC, a lethal stage of prostate cancer associated with increased morbidity, mortality and healthcare costs.[7, 9, 10, 52] The current standard of care in both settings is inadequate given the level of pharmaceutical innovation available; a new, simple, oral treatment regimen is needed that can delay disease progression, prolong survival and maintain patients' HRQL. Although not captured in the cost per quality adjusted life year (QALY) analysis, the expected benefits of an effective treatment in terms of psychological impact and caregiver burden are significant. Indeed, the need for an alternative option is more acute than ever as treatment guidelines across the globe advise against the use of docetaxel for mHSPC during the COVID-19 pandemic, due to the risk of neutropenia and frequent hospital visits with chemotherapy. [34] The value of simplifying disease management and reducing overall

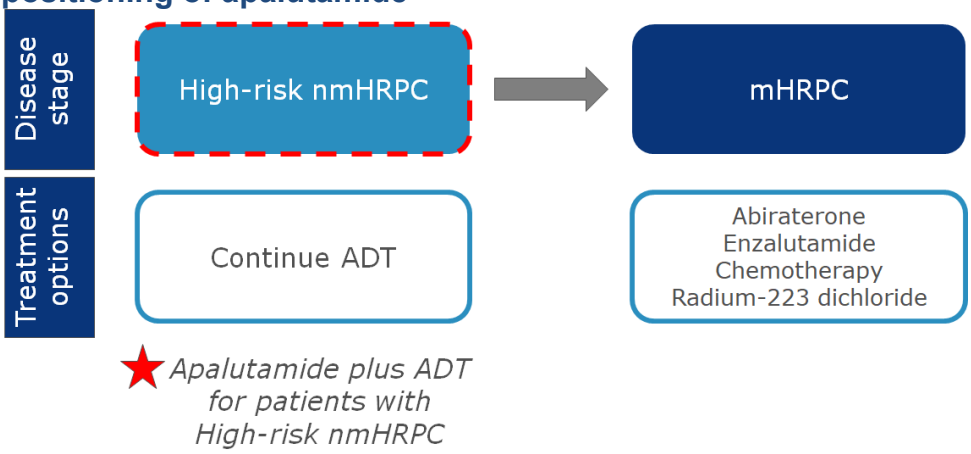
strain on NHS capacity and resources during and beyond the COVID-19 pandemic should not be underestimated and is not intrinsically captured in the cost per QALY framework.

A.3 Clinical pathway of care

A.3.1 Pathway of care for high-risk nmHRPC

Clinical guidelines for the management of prostate cancer are available from NICE[20], the European Association of Urology (EAU)[21] and the European Society for Medical Oncology (ESMO).[53] The EAU guideline recommends that patients with high-risk nmHRPC be offered either apalutamide, darolutamide or enzalutamide.[21] However, none of these treatments have yet been recommended for use in the NHS. Neither the NICE nor ESMO guidelines provide explicit recommendations for the high-risk nmHRPC population, meaning that this population currently has no treatment options available other than the continuation of ADT (Figure 5).

Figure 5: Current treatment pathway for high-risk nmHRPC in the UK and positioning of apalutamide

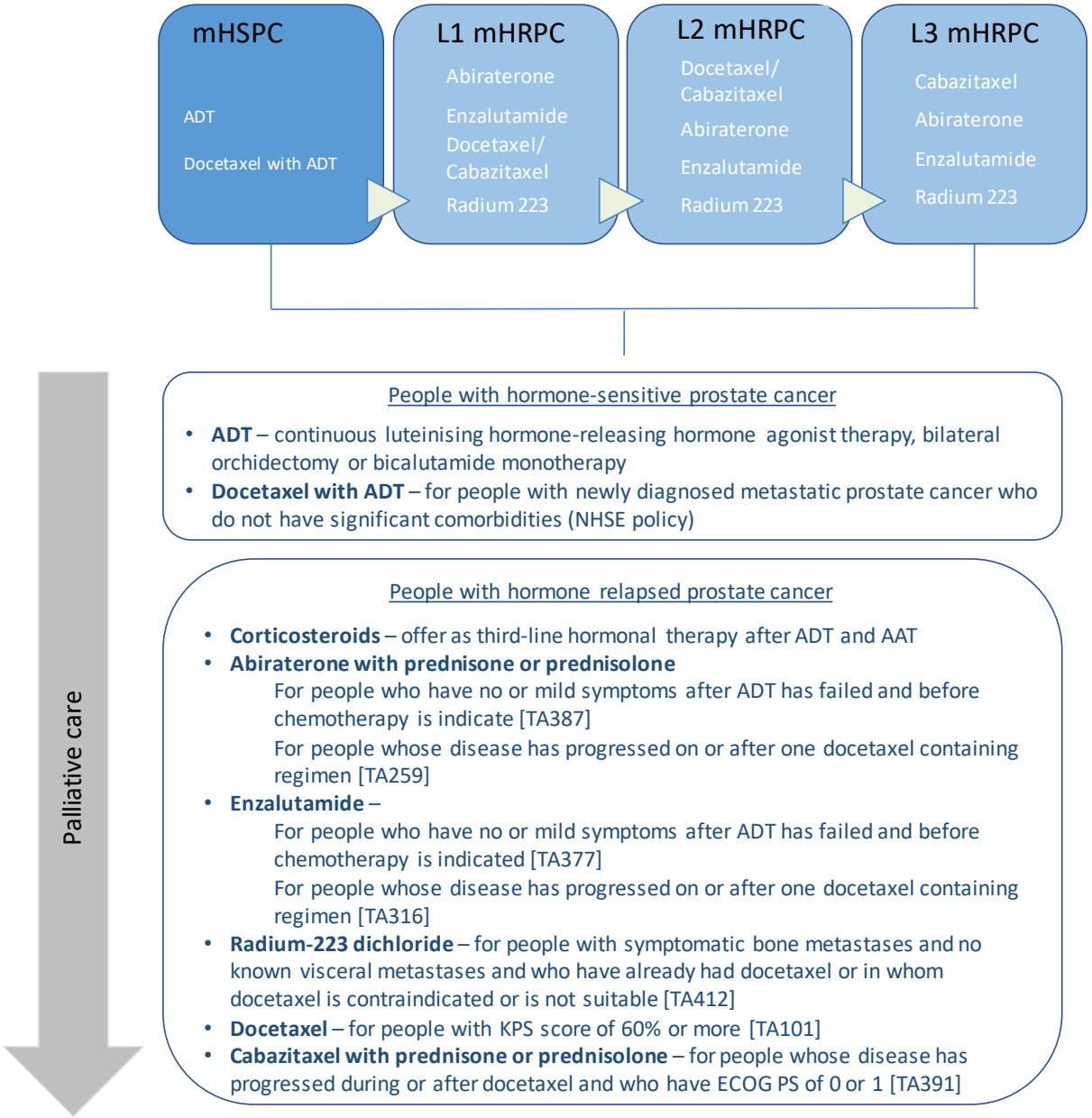


Abbreviations: ADT: androgen-deprivation therapy; nmHRPC: non-metastatic hormone-relapsed prostate cancer; mHRPC: metastatic hormone-relapsed prostate cancer.
Source: NICE CG131[20], NICE TA387[54], NICE TA377[55], NICE TA412.[56]

A.3.2 Pathway of care for mHSPC

Figure 6 summarises the clinical pathway of care for mHSPC, according to the NICE guideline for prostate cancer diagnosis and management (NG131).

Figure 6: Clinical pathway of care for metastatic prostate cancer



Abbreviations: AAT: anti-androgen therapy; ADT: androgen deprivation therapy; ECOG: Eastern Cooperative Oncology Group; KPS: Karnofsky performance status; L: line; mHRPC: metastatic castrate-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; NHSE, NHS England; PS: performance status; TA, technology appraisal.
Notes: NHS England has restricted the funding of novel agents such that a single patient cannot receive more than one novel agent throughout the course of their disease.
Source: Adapted from the NICE guideline for prostate cancer diagnosis and management.[20]

As can be seen from this pathway, treatment options for mHSPC in current practice include ADT and docetaxel plus ADT with the following restriction:

- Docetaxel should be offered to people with newly diagnosed metastatic prostate cancer who do not have significant comorbidities

Abiraterone with prednisolone plus ADT was “not recommended” in the NICE final appraisal document published in June 2020. Enzalutamide plus ADT is currently

undergoing a NICE appraisal. Thus, neither treatment is part of standard NHS clinical practice.

Therefore, patients with mHSPC who are ineligible for chemotherapy only have a single treatment option in current practice – ADT.

A.3.3 Chemo-ineligibility in mHSPC

A large proportion of the mHSPC patient population is currently being treated with ADT alone. The national prostate cancer audit estimates that only 27% of newly diagnosed metastatic prostate cancer patients receive docetaxel.[19] These data are supported by clinical expert opinion, which suggests that only 30% of all mHSPC patients receive docetaxel.[57] This means that up to 73% of mHSPC patients are ineligible or otherwise unsuitable for chemotherapy. The annual incidence for mHSPC in England is 9,629 (see Appendix M of document B). Thus, 7,029 patients are currently unsuitable for chemotherapy.

A patient's eligibility for receiving upfront chemotherapy is multi-factorial and extends beyond just contraindications to docetaxel.

Age is an important determinant of eligibility, with older patients less likely to receive chemotherapy than other age groups. A report prepared by Prostate Cancer UK concluded that 64% of patients in the 69 years or younger age group diagnosed with metastatic disease received chemotherapy in 2016. In stark contrast, the uptake for chemotherapy was much lower for the over 80 years age group at only 6%. This is impactful, as the incidence of mHSPC is highest in the latter age group.[58]

Changes in clinical guidance in response to the COVID-19 pandemic have reduced further the proportion of patients receiving chemotherapy. EAU guidelines state that docetaxel plus ADT should be avoided in mHSPC patients. This is based on the risk of neutropenia and the risk of infection due to frequent hospital visits during the pandemic.[34] Cancer Research UK estimates that the impact of the COVID-19 disease is such that the proportion of patients receiving chemotherapy (including those with conditions other than prostate cancer) in England has reduced by 30%.[59] COVID-19 has reduced the already stretched capacity of the NHS to manage patients with cancer and is likely to have a long-term impact on the NHS's ability to meet the demand for cancer diagnosis and treatment.[59]

In conclusion, an overwhelming majority of mHSPC patients are currently being managed with ADT alone. Among these patients, older people are at an unfair disadvantage as they are least likely to be eligible for chemotherapy and, thus, are more likely to suffer poorer clinical outcomes. Furthermore, due to COVID-19, the size of the chemo-ineligible cohort has increased as treatment centres have suspended the use of chemotherapy even for eligible patients, as advised by the new guidelines. It is therefore of benefit for clinicians to have an additional treatment option. This would permit individualised treatment based on the unique patient

profile, particularly in the disadvantaged older patient population, and provide the best chance of extended survival.

A.4 Equality considerations

As in previous appraisals for technologies for treating prostate cancer, recommendations should apply to adults with prostate cancer, because men and transgender women have a prostate.

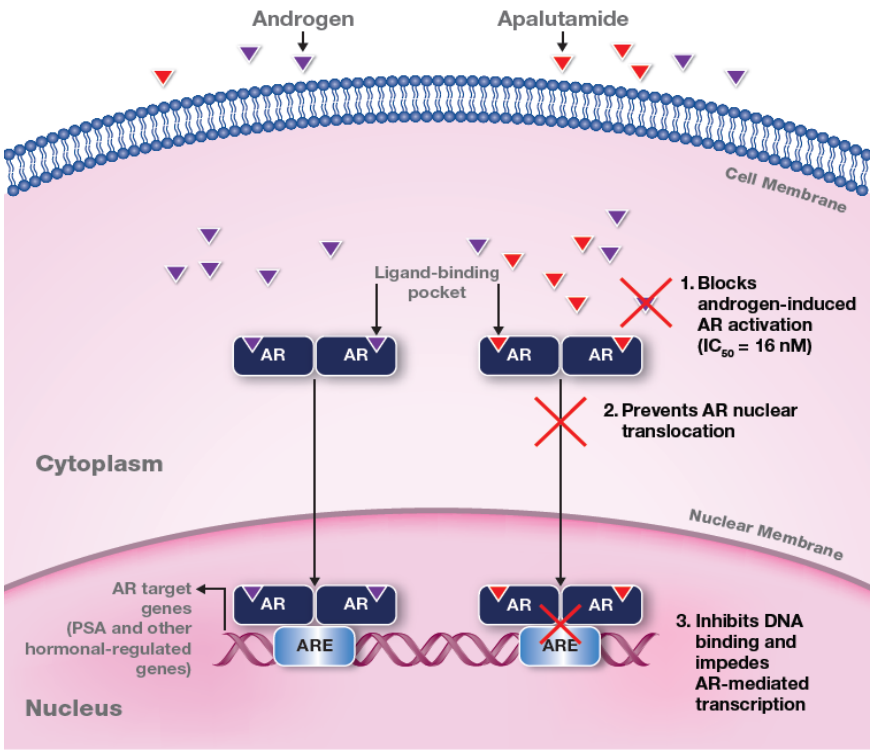
As discussed in Section A.3 a substantial proportion of mHSPC patients do not receive chemotherapy and would benefit from the availability of an additional treatment option capable of extending survival while preserving HRQL. This proportion is driven by older patients. Data covering the period 2013–2016 demonstrates that only 6% of men over 80 and only 26% of men between 75 and 79 received chemotherapy.[58] This situation raises the prospect of patients being disproportionately disadvantaged on the basis of age.

A.5 The technology

A summary of the mechanism of action, marketing authorisation, costs and administration requirements for apalutamide is presented in Table 1.

Table 1:Technology being appraised

UK approved name and brand name	Apalutamide (Erleada®).
Mechanism of action	Apalutamide is an orally bioavailable, second-generation non-steroidal anti-androgen that targets the androgen receptor with high affinity and competitively inhibits androgen binding to the ligand-binding domain.[60] It thereby blocks androgen-induced androgen receptor activation, prevents nuclear translocation, inhibits DNA binding and impedes androgen receptor-mediated transcription (Figure 7). By repressing the expression of androgen-regulated genes that are crucial for prostate tumour viability and growth, apalutamide has an immediate and durable impact on PSA levels[4] and inhibits prostate tumour progression.[61] In contrast to first-generation anti-androgens (e.g. bicalutamide), apalutamide selectively and irreversibly binds to the androgen receptor with high affinity and exhibits minimal binding to other hormonal and neurotransmitter receptors.[61]

	Figure 7: Mechanism of action of apalutamide[61]  **Abbreviations:** AR: androgen receptor; ARE: androgen response element; DNA: deoxyribonucleic acid; IC_{50}: half maximal inhibitory concentration; PSA: prostate-specific antigen.
Marketing authorisation/CE mark status	Positive CHMP opinion for apalutamide in the treatment of adult men with high-risk nmHRPC was received on 15 November 2018 and marketing authorisation was subsequently granted on 16 January 2019.[1] For adult men with mHSPC, positive CHMP opinion was received on 13 December 2019 and marketing authorisation was granted on 29 January 2020.[1]
Indications and any restriction(s) as described in the summary of product characteristics	Apalutamide is indicated:[1] • In adult men for the treatment of nmHRPC who are at high risk of developing metastatic disease • In adult men for the treatment of mHSPC in combination with ADT
Method of administration and dosage	Apalutamide is administered orally as a single daily dose of 240 mg (given as four 60 mg tablets) taken with or without food. Apalutamide is administered in combination with ADT.
Additional tests or investigations	No routine monitoring requirements are associated with apalutamide.

<table>
<tr><td>List price and average cost of a course of treatment</td><td>The NHS list price of apalutamide 60 mg × 112 tablets = £2,735. In both indications, treatment is continued until disease progression. The cost of a course of treatment per patient per year is shown in the table below.<table><tr><td>Pack cost (list price)</td><td>£2,735 for 28 days</td></tr><tr><td>Packs per year</td><td>365/28 = 13[a]</td></tr><tr><td>Drug cost per patient per year[b]</td><td>£35,653</td></tr></table>[a] Rounded to the nearest integer. All calculations in the table were performed from exact, unrounded values. [b] Maximum drug cost presented, assuming all patients who are initiated on apalutamide stay on treatment for a full year.</td></tr>
<tr><td>Patient access scheme (if applicable)</td><td>A patient access scheme representing a simple discount of [redacted] from the list price of apalutamide has been included in this submission.</td></tr>
</table>

Abbreviations: ADT: androgen-deprivation therapy; CHMP: Committee on Human Medicinal Products; EMA: European Medicines Agency; GnRH: gonadotropin-releasing hormone; HRQL: health-related quality of life; nmHRPC: non-metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; PSA: prostate-specific antigen; PSADT: prostate-specific antigen doubling time.
Note. Castration-resistant prostate cancer is referred to as hormone-relapsed prostate cancer in this submission to align with the terminology used in the NICE final scope.[62]

A.6 Decision problem and NICE reference case

The objective of this appraisal is to determine the clinical and cost effectiveness of apalutamide within its full marketing authorisation in nmHRPC (high-risk) and mHSPC.

Details of how the company submission differs from the final NICE scope with respect to the population, included comparators and outcomes assessed are presented in Table 2.

Table 2: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population			
nmHRPC	Adults with nmHRPC	Adults with high-risk nmHRPC	The marketing authorisation of apalutamide in nmHRPC is for those at high risk of developing metastatic disease*, as per the SPARTAN registrational trial.
Comparator(s)			
mHSPC	• ADT • Docetaxel with ADT • Abiraterone with prednisolone or prednisolone and ADT (subject to ongoing NICE appraisal) • Enzalutamide with ADT (subject to ongoing NICE appraisal)	• ADT • Docetaxel with ADT	• Abiraterone was not recommended in the NICE FAD released in June 2020. As such, it cannot be considered a relevant comparator • Enzalutamide with ADT is currently being appraised by NICE. As such, it cannot be considered a relevant comparator
Outcomes			
nmHRPC	The outcome measures to be considered include: • OS • PFS • Response rate • PSA response • Adverse effects of treatment • HRQL	The outcome measures to be considered include: • OS • PFS • PSA response • Adverse effects of treatment • HRQL measures • MFS • Time to symptomatic progression • Time to PSA progression	Outcome measures to be considered are as per the scope, and additional outcome measures provide supportive efficacy data for apalutamide.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		• PFS2 • Time to initiation of cytotoxic chemotherapy • Time to metastasis	
mHSPC	The outcome measures to be considered include: • OS • PFS • Response rate • PSA response • Adverse effects of treatment • HRQL	The outcome measures to be considered include: • OS • rPFS • PFS • PSA response • Adverse effects of treatment • HRQL • PFS2	Outcome measures to be considered are as per the scope, and additional outcome measures provide supportive efficacy data for apalutamide.
Subgroups of interest			
mHSPC	• people with newly diagnosed metastatic prostate cancer • people with high-risk metastatic prostate cancer	• patients ineligible or unsuitable for chemotherapy	Unmet need is highest in these patients

Abbreviations: ADT: androgen-deprivation therapy; FAD: final appraisal document; HRQL: health-related quality of life; MFS: metastases-free survival; mHSPC: metastatic hormone-sensitive prostate cancer; nmHRPC: non-metastatic hormone-relapsed prostate cancer; OS: overall survival; PSA: prostate specific antigen; PFS: progression-free survival; PFS2: second progression-free survival; rPFS, radiographic progression-fee survival.
Source: NICE 2020. Final scope for the appraisal of apalutamide for treating prostate cancer.[62]
Notes: * a high risk for the development of metastases is defined as PSADT ≤10 months during continuous ADT

A.7 Clinical effectiveness evidence

Evidence of the clinical effectiveness of apalutamide plus ADT is derived from SPARTAN and TITAN. These were Phase III, multicentre, randomised, double-blind, controlled studies comparing apalutamide plus ADT with placebo plus ADT among patients with high-risk nmHRPC and mHSPC, respectively (Table 3). Placebo plus ADT is a directly relevant comparator representing standard of care for high-risk nmHRPC and mHSPC patients in England. (59)

Table 3: Clinical effectiveness evidence

Study	SPARTAN (NCT01946204)	TITAN (NCT02489318)
Study design	A Phase III randomised, placebo-controlled, double-blinded study of apalutamide plus ADT versus placebo plus ADT in patients with nmHRPC (high-risk)	A Phase III randomized, placebo-controlled, double-blinded study of apalutamide plus ADT versus placebo plus ADT in patients with mHSPC.
Population	Adult men with histologically or cytologically confirmed adenocarcinoma of the prostate that was hormone-relapsed, and who were at high risk for the development of metastasis (defined as PSADT ≤ 10 months during continuous ADT)	Adult patients with a diagnosis of prostate adenocarcinoma and metastatic disease documented by ≥ 1 bone lesion(s) on Technetium-99m (^{99m}Tc) bone scan.
Intervention(s)	Apalutamide 240 mg once daily plus ADT (n = 806)	Apalutamide 240 mg once daily plus ADT (n = 525)
Comparator(s)	Placebo plus ADT (n = 401)	Placebo plus ADT (n = 527)
Indicate if trial supports application for marketing authorisation	Yes	Yes
Indicate if trial used in the economic model	Yes	Yes
Rationale for use/non-use in the model	Provides direct head-to-head evidence of the clinical safety and efficacy of apalutamide plus ADT versus ADT therapy alone in high-risk nmHRPC patients	Provides direct head-to-head evidence of the clinical safety and efficacy of apalutamide plus ADT versus ADT therapy alone in mHSPC patients
Reported endpoints specified in the decision problem	MFS (**primary endpoint**) OS PSA response Adverse effects of treatment Health-related quality of life	OS (**co-primary endpoint**) rPFS (**co-primary endpoint**) Response rate PSA response Adverse effects of treatment Health-related quality of life

All other reported endpoints	TTM PFS Time to symptomatic progression Time to initiation of cytotoxic chemotherapy PFS2 Time to PSA progression	Time to cytotoxic chemotherapy Time to pain progression Time to chronic opioid use Time to SRE Time to PSA progression PFS2 Prostate cancer-specific survival Time to ECOG PS deterioration Time to symptomatic local progression

Abbreviations: ADT: androgen deprivation therapy; ECOG: Eastern Cooperative Oncology Group; MFS: metastases-free survival; mHSPC: metastatic hormone-sensitive prostate cancer; nmHRPC: non-metastatic hormone-relapsed prostate cancer; PFS: progression-free survival; PFS2: second progression-free survival; PS, performance status; PSA: prostate-specific antigen; PSADT: prostate-specific antigen doubling time; SRE: skeletal related events; TTM: time to metastasis.
Source: Smith et al. (2018)(4) and Chi (2019)(60)

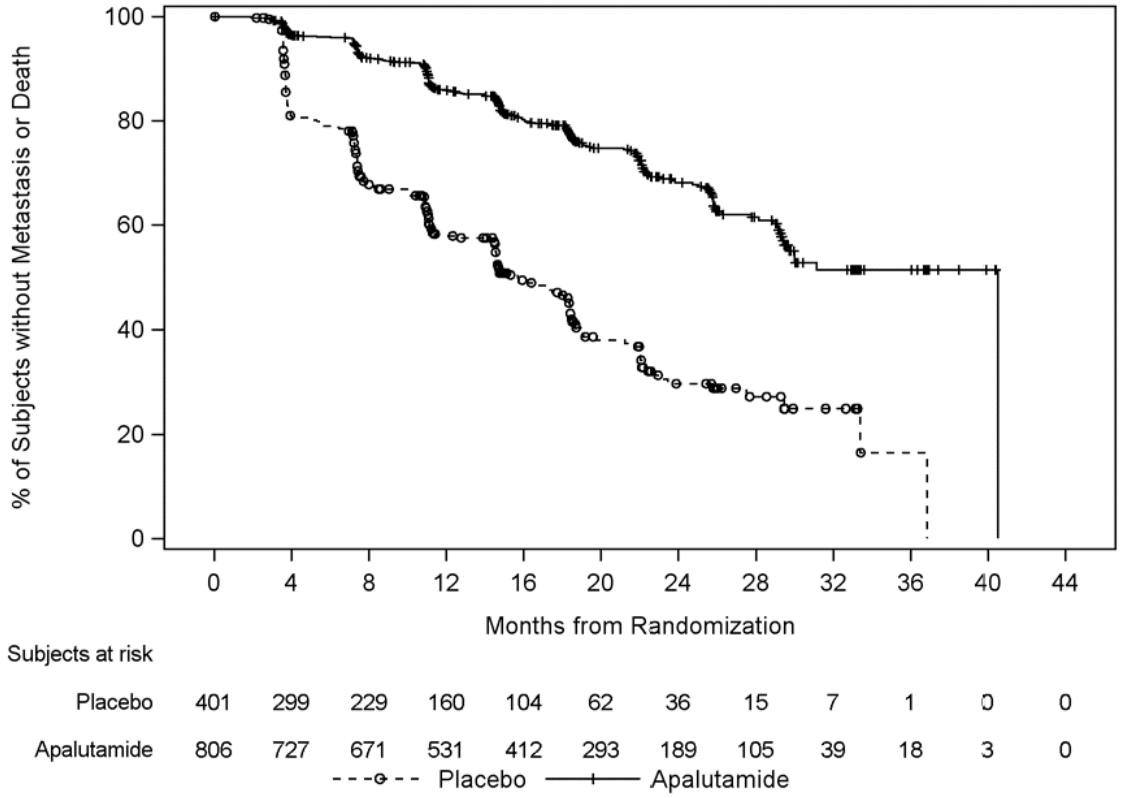
A.8 Key results from the clinical effectiveness evidence

The clinical benefit of apalutamide plus ADT versus current standard of care for nmHRPC (high-risk) and mHSPC is clearly demonstrated in the results from SPARTAN and TITAN. Compared with ADT alone, apalutamide plus ADT has demonstrated a statistically significant benefit on the risk of progression or death. Progression is measured by metastases-free survival (MFS) and radiographic progression-free survival (rPFS) in nmHRPC (high-risk) and mHSPC, respectively. Moreover, apalutamide has demonstrated a significant OS benefit in patients with high-risk nmHRPC and with mHSPC.[6, 12] Apalutamide not only delays progression and improves survival, it also delays the associated symptomatic sequelae of progression (such as pain), delays the need for cytotoxic chemotherapy and increases time spent with a good quality of life compared with standard of care.[4, 6]

A.8.1 Metastases-free survival (SPARTAN only – primary endpoint)

MFS was defined in SPARTAN as the time from randomisation to the time of first evidence of blinded independent central review (BICR) confirmed bone or soft tissue distant metastasis or death due to any cause, whichever occurred first. As shown in Figure 8, after a median follow-up of 20.3 months, treatment with apalutamide plus ADT significantly reduced the risk of disease progression or death by 70% compared with placebo plus ADT (hazard ratio [HR] = 0.30, 95% confidence interval [CI]: 0.24, 0.36; $p < 0.0001$). Median MFS was 40.5 months in the apalutamide group and 15.7 months in the placebo group. On average, patients receiving apalutamide plus ADT, therefore, have 24.3 months longer than those receiving placebo plus ADT before developing metastases,[4]which are associated with a worse prognosis and declining HRQL.

Figure 8: Kaplan–Meier plot for MFS in SPARTAN

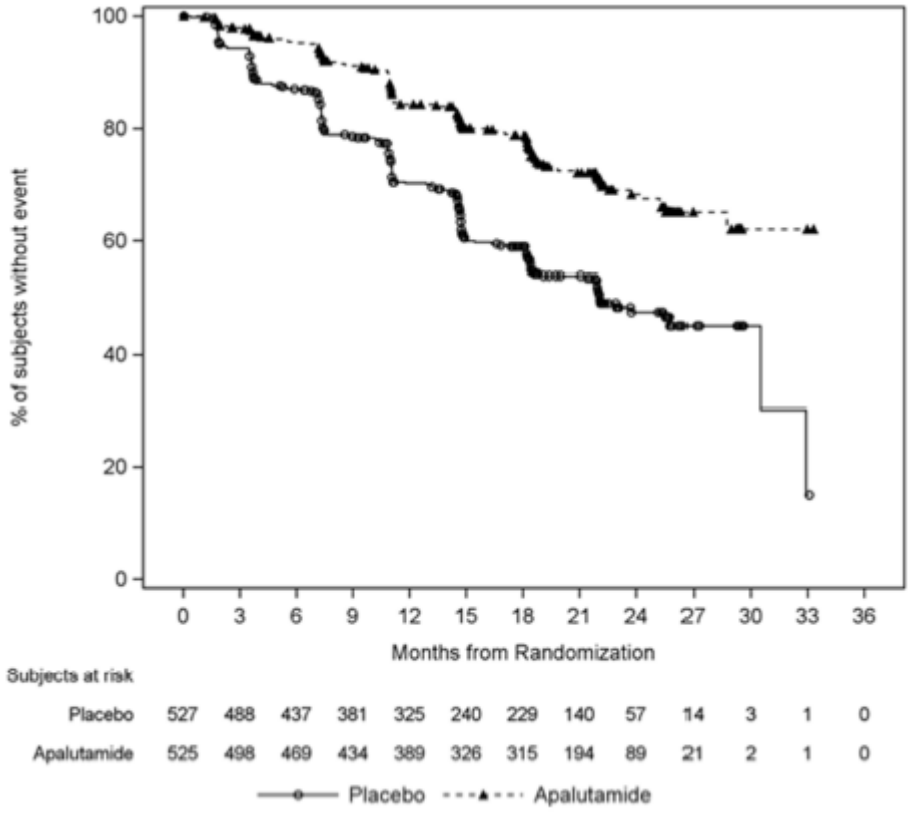


Abbreviations: BICR: blinded independent central review; FA: final analysis; ITT: intention to treat; MFS: metastases-free survival.
Source: Summary of BICR MFS in SPARTAN (clinical cut-off date 19th May 2017; ITT population, SPARTAN CSR.[63]

A.8.2 Radiographic progression-free survival (TITAN only – co-primary endpoint)

rPFS as assessed by the investigator was defined in TITAN as the duration from the date of randomisation to the date of first documented radiographic progressive disease or death due to any cause, whichever occurred first. As shown in Figure 9, after a median follow-up of 22.7 months, treatment with apalutamide plus ADT significantly reduced the risk of disease progression or death by approximately 52% compared with placebo plus ADT (HR = 0.48, 95% CI: 0.39, 0.60; p < 0001). Median rPFS was not reached in the apalutamide plus ADT arm and was 22.1 months in the placebo plus ADT arm. The percentage of patients with rPFS at 24 months was 68.2% in the apalutamide group and 47.5% in the placebo group. This demonstrates that mHSPC patients receiving apalutamide plus ADT are significantly less likely to suffer disease progression to the mHRPC disease stage, which is associated with worsening prognosis and a decline in HRQL[6]

Figure 9: Kaplan–Meier plot for rPFS in TITAN



Abbreviations: CSR: clinical study report; ITT: intention to treat; rPFS: radiographic progression-free survival.
Source: *Figure 4: Kaplan–Meier Plot of rPFS; ITT Population (Study 56021927PCR3002)*, TITAN CSR.[61]

A.8.3 Overall survival (SPARTAN and TITAN [co-primary endpoint])

Treatment with apalutamide plus ADT resulted in statistically significant improvements in OS compared with placebo plus ADT in both the SPARTAN and TITAN trials (see Figure 10).

In SPARTAN, at final analysis, after 52.0 months median follow-up, 428 death events had been observed (274 [34.0%] in the apalutamide plus ADT arm and 154 [38.4%] in the placebo plus ADT arm). Treatment with apalutamide plus ADT significantly decreased the risk of death by 22% compared with placebo plus ADT (HR 0.78; 95% CI 0.64, 0.96), two-sided p = 0.016). Median OS was 73.9 months and 59.9 months in the apalutamide plus ADT and placebo plus ADT arms, respectively.

In England, treatment for prostate cancer is limited to only one novel therapy. According to this rule, one novel therapy is allowed as a subsequent therapy in the placebo plus ADT arm, and not in the apalutamide plus ADT arm. However, in SPARTAN, [redacted] Moreover, 76 patients (19% of the randomised placebo plus ADT patients) crossed over to the apalutamide plus ADT arm at the time of study unblinding.

Therefore, in view of the treatment pathway in England, the analysis for OS may be biased because both arms are affected by non-permitted sequences. Additionally, the placebo plus ADT arm may have gained survival time attributed to apalutamide during cross-over

As such, adjustment for the affected subsequent treatments was necessary to reduce bias and increase the generalisability of trial results to English clinical practice. All methods recommended in NICE decision support unit (DSU) technical support document (TSD) 16[64] to adjust for such bias were explored. However, the complexities of the data and the array of treatment switches meant that it was only possible to implement adjustment using rank preserving structural failure time modelling (RPSFTM). For a full discussion of the rationale for selecting RPSFTM methodology, please see Appendix R in Document B. Following adjustment using RPSFTM, the OS HR was [redacted] for apalutamide plus ADT versus placebo plus ADT, indicating minimal bias in the trial results against apalutamide.

In TITAN, at the time of the first interim analysis, after a median follow-up of 22 months, a total of 200 deaths were observed; 83 (15.8%) in the apalutamide plus ADT arm and 117 (22.2%) in the placebo plus ADT arm. Treatment with apalutamide plus ADT significantly improved OS with a 33% reduction in the risk of death compared with placebo plus ADT (HR 0.67; 95% CI: 0.51, 0.89; p = 0.0053). Median OS was not reached in either arm. The OS survival percentage at 24 months was 82.4% in the apalutamide plus ADT arm and 73.5% in the placebo plus ADT arm.

Based on the first interim analysis of TITAN, [redacted] received a second novel subsequent therapy. [redacted] received a second novel therapy. As additional data covering the trial period post unblinding is not yet available, the data used to inform this submission are unaffected by confounding due to cross-over (from placebo to apalutamide).

The RPSFTM and the inverse probability of censored weights (IPCW) methods were deemed suitable to explore the adjustment for the one novel subsequent therapy rule in TITAN. Following the adjustment, the OS benefit of apalutamide plus ADT versus placebo plus ADT was comparable to the ITT-analysis with the following hazard ratios for apalutamide plus ADT versus placebo plus ADT:

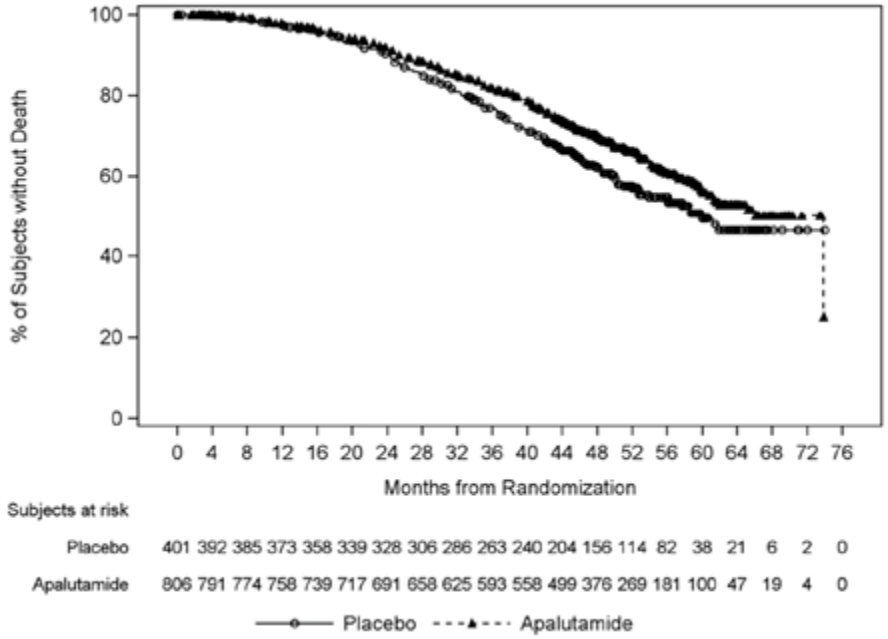
[redacted]

As only a limited number of patients both from the active and the control arm switched to treatments not permitted in the English context, the adjustment of OS using both IPCW and RPSFTM had very limited impact, with the adjusted results

being nearly similar to the unadjusted ones. Details are presented in Appendix R of Document B.

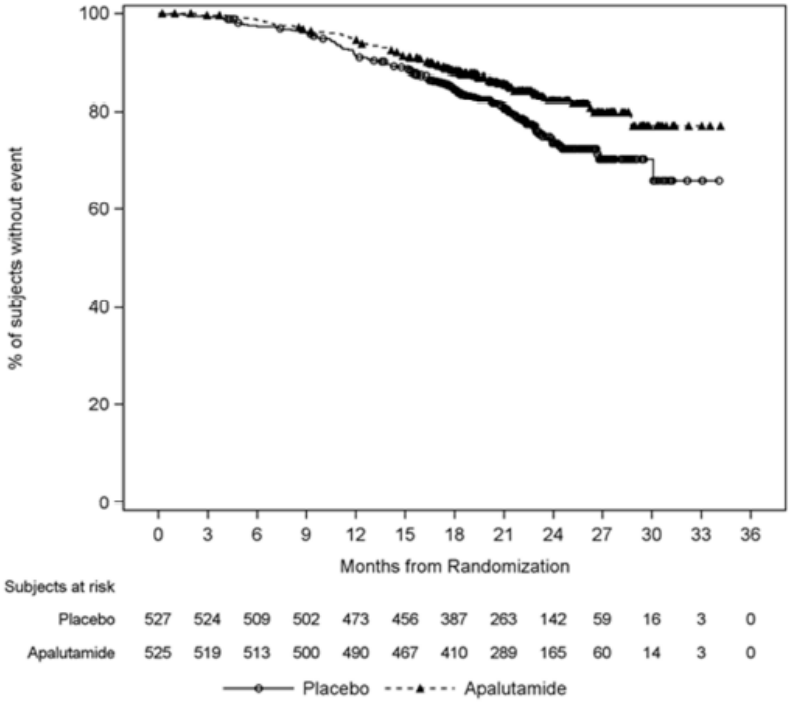
Figure 10: Kaplan–Meier plot for OS in SPARTAN and TITAN

1 SPARTAN



Source: SPARTAN final analysis: clinical cut-off date 1st February 2020; ITT population, SPARTAN FA CSR[63]

2 TITAN



Source: *Figure 2: Kaplan-Meier Plot of OS; ITT Population (Study 56021927PCR3002),* TITAN CSR[61]

Abbreviations: CSR, clinical study report; FA, final analysis; ITT, intention to treat; OS, overall survival;

A.8.4 Second progression-free survival (SPARTAN and TITAN)

PFS2 was defined in SPARTAN and TITAN as the time from randomisation to investigator-assessed disease progression with the first subsequent therapy or death. Treatment with apalutamide plus ADT resulted in significant improvements in PFS2 compared with placebo plus ADT in both trials.

In SPARTAN, apalutamide extended median PFS2 by 14.4 months versus placebo plus ADT. In the apalutamide plus ADT arm, 319 (39.6%) patients experienced progression on or after first subsequent therapy or death (PFS2), compared with 190 patients in the placebo plus ADT arm (47.4%). Treatment with apalutamide plus ADT was associated with a 45% reduction in the risk of disease progression or death on the first subsequent treatment compared with placebo plus ADT (HR = 0.55; 95% CI: 0.46, 0.66; p < 0.0001).

Adjusting PFS2 for the one novel therapy rule followed the same methodology as described for OS in Section A.8.3. Following adjustment using RPSFTM, the PFS2 HR was [redacted]) for apalutamide plus ADT versus placebo plus ADT. Further details of the analysis are presented in Appendix R of Document B.

In TITAN, treatment with apalutamide plus ADT significantly delayed the time to disease progression or death on the first subsequent treatment in patients with mHSPC when compared with placebo plus ADT. A total of 209 events were observed: 88 (16.8%) in the apalutamide plus ADT arm and 121 (23.0%) in the ADT arm. Median PFS2 was not reached in either arm. Treatment with apalutamide plus ADT was associated with a 34% reduction in the risk of disease progression or death on the first subsequent treatment compared with placebo plus ADT (HR = 0.66; 95% CI: 0.50, 0.87; p < 0.0026).

Adjusting PFS2 for the one novel therapy rule following the same methodology as described for OS in Section A.8.3 showed the following hazard ratios:

[redacted]

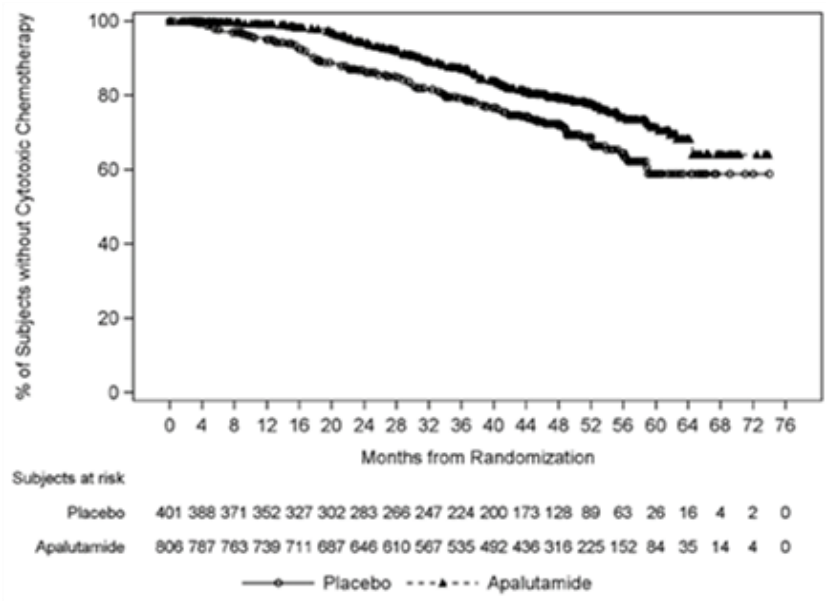
As with OS, the PFS2 benefit of apalutamide plus ADT versus ADT alone following adjustment were similar to or suggested a greater benefit for patients treated with apalutamide plus ADT than the unadjusted results.

The results from both trials are presented in Figure 11.

The observed statistically significant improvement in PFS2 with apalutamide plus ADT demonstrates that long-term outcomes were improved versus waiting to use a novel therapy in mHRPC.

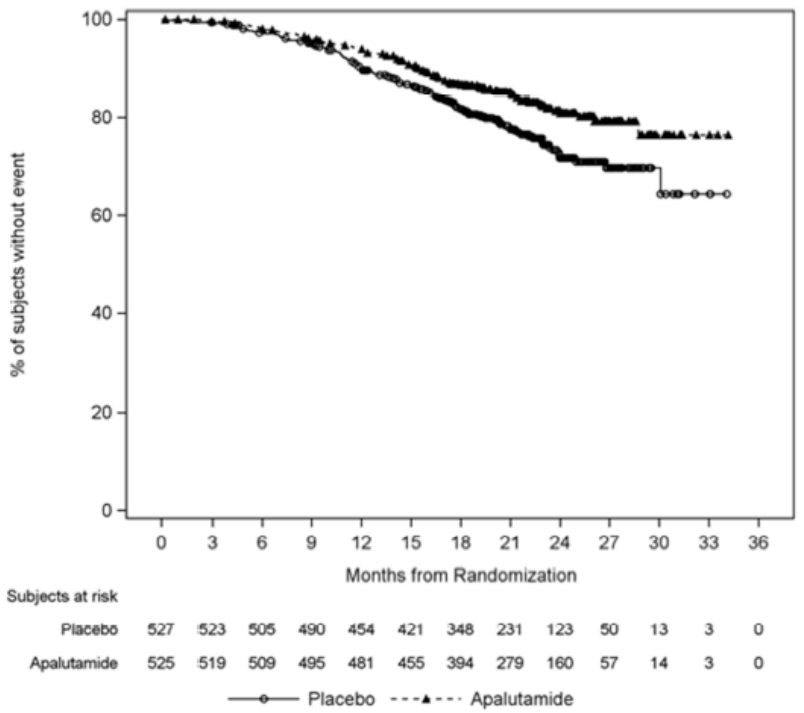
Figure 11: Kaplan–Meier plot for PFS2 in SPARTAN and TITAN

1 **SPARTAN**



Source: SPARTAN final analysis: clinical cut-off date 1 February 2020; ITT population, FA CSR.[63]

2 **TITAN**



Source: Figure 8: Kaplan–Meier Plot of PFS2; ITT population (Study 56021927PCR3002), TITAN CSR.[61]

Abbreviations: CSR, clinical study report; FA, final analysis; ITT, intention to treat; PFS2, second progression-free survival.

A.8.5 Patient-reported outcomes (SPARTAN and TITAN)

For patients with nmHRPC and mHSPC, the physical burden of disease is typically low and comparable with that of the general population, although some patients may experience symptoms caused by both their disease and treatment with ADT.[13, 65] As noted in Section A.2 , once patients progress to mHRPC, HRQL rapidly decreases. As such, it is important that any treatments patients receive ahead of mHRPC extend progression-free survival (PFS) and preserve HRQL.

HRQL was assessed until end of treatment and for up to 12 months post-progression in both trials via the generic EQ-5D® questionnaire, with SPARTAN using the three-level scale (EQ-5D-3L) and TITAN using the five-level scale (EQ-5D-5L). The compliance rates were good for both trials and were similar across treatment groups. For SPARTAN, the completion rate of the EQ-5D-3L questionnaire for ≥ 50% items was 95% or greater (range 95.4%–100%) at any assessment visit during the treatment phase (baseline to Cycle 29). For TITAN, compliance ranged from 75%–85% from baseline to Cycle 13 and remained near 80% thereafter.

Across both trials, baseline EQ-5D index and visual analogue scale scores were comparable across both treatment arms and, importantly, HRQL was maintained in patients until cycle 29 of treatment in SPARTAN and throughout the treatment phase in TITAN.

A.8.6 Safety

Overall, apalutamide plus ADT was well tolerated and demonstrated a manageable safety profile that was similar to that of placebo plus ADT. This is consistent with the results presented in Section A.8.5, which show that HRQL was preserved throughout the treatment phase in patients receiving apalutamide plus ADT. These results are important given that patients with nmHRPC and mHSPC are generally asymptomatic, and there is an unmet need for a novel therapy that is well tolerated and able to maintain HRQL ahead of progression to mHRPC.

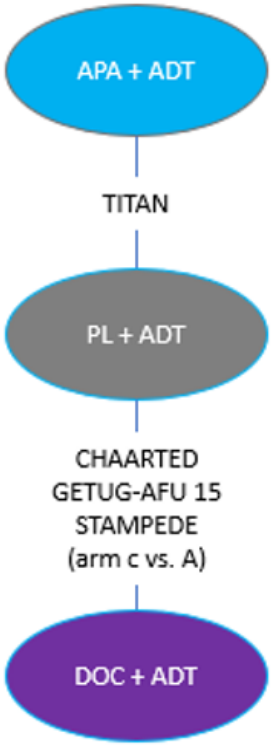
A.9 Evidence synthesis

Both SPARTAN and TITAN provide randomised, robust, comparative evidence of apalutamide plus ADT versus placebo plus ADT. Therefore, it was not necessary to conduct any form of indirect treatment comparison against ADT. However, external evidence was used to estimate the long-term OS extrapolation of ADT alone via an informed fits analysis (see Section A.5 and Section B.3.3 of Document B).

For comparison against docetaxel plus ADT in the mHSPC population, direct evidence was not available, so an indirect treatment comparison in the form of a Bayesian network meta-analysis (NMA) was carried out to compare clinical outcomes of apalutamide with docetaxel. The trials that were included in the NMA were: CHAARTED, GETUG-AFU15, STAMPEDE (including published data and

unpublished individual patient data) and TITAN, which were linked by ADT alone as the common comparator (Figure 12).

Figure 12. Evidence network



Abbreviations: ADT, androgen deprivation therapy; APA, apalutamide; DOC, docetaxel; PL, placebo.

For rPFS, treatment with apalutamide plus ADT had a [redacted] probability of improving rPFS versus docetaxel plus ADT ([redacted]). For OS, treatment with apalutamide plus ADT had a [redacted] probability of improving OS versus docetaxel plus ADT ([redacted]).

In terms of safety, the odds of experiencing any adverse events (AEs) were [redacted] with apalutamide plus ADT versus docetaxel plus ADT ([redacted]). The odds of a serious adverse event were [redacted] with apalutamide plus ADT compared to docetaxel plus ADT ([redacted]). Given the strong patient preference for treatments that extend life without impacting quality of life, these results highlight the suitability of apalutamide as a treatment option for all mHSPC patients.

For more details of the NMA, see Section B.2.19 of Document B.

A.10 Key clinical issues

SPARTAN and TITAN are well-conducted Phase III randomised controlled trials of apalutamide plus ADT compared with the directly relevant standard of care (ADT alone) in nmHRPC (high-risk) and mHSPC. Data from the national prostate cancer

audit demonstrate that ADT alone is standard of care in mHSPC.(38) Moreover, age is an important determinant of the uptake of chemotherapy, with older patients (≥ 75 years of age) significantly less likely to receive chemotherapy. Incidence rates for prostate cancer in the UK are highest in patients aged 75 to 79. [18]

A.10.1 Data immaturity

SPARTAN and TITAN provide robust data to allow for a comparison between apalutamide plus ADT and ADT alone. Median MFS, PFS2 and OS have been reached in SPARTAN; however, TITAN data are currently immature.

For SPARTAN, median MFS in the apalutamide plus ADT arm was 40.51 months, which was close to the median PFS2 of the placebo plus ADT arm at 45.21 months. This highlights that when half of the patients treated with apalutamide plus ADT remained metastases-free, nearly half of patients treated with placebo plus ADT had already developed metastases and progressed on their first effective subsequent therapy for mHRPC.

Median PFS2 has not been reached in the TITAN trial, so this comparison cannot yet be made for mHSPC patients. However, the HR for PFS2 indicates that time to secondary progression or death was significantly lower for apalutamide plus ADT patients versus placebo plus ADT patients (HR = 0.66; 95% CI: 0.50, 0.87; p = 0.0026.

This supports the case for earlier treatment in nmHRPC (high-risk) and mHSPC, demonstrating that long-term outcomes are improved versus waiting to use a novel treatment in mHRPC.

A.10.2 Subsequent therapies

Treatment with a novel agent was offered to patients who had progressed in both SPARTAN and TITAN, regardless of initial treatment. These treatments are known to prolong survival but would only be used once in a patient's treatment pathway in the UK due to NHS England's one novel therapy commissioning policy. Therefore, OS and PFS2 data were adjusted to remove the confounding effect on survival of receiving two or more novel therapies and to increase the generalisability of the efficacy data to UK clinical practice. This adjustment applied the methods outlined in NICE DSU TSD 16 that are typically used to account for bias caused by treatment switching. The analysis conducted for nmHRPC demonstrated that the adjustment had a small impact on survival outcomes, while the analysis for mHSPC failed to demonstrate any significant impact. Details of the results of this adjustment are presented in Section B

A.10.3 Comparisons to docetaxel

The comparison of apalutamide plus ADT with docetaxel plus ADT relied on an NMA because direct evidence was not available. The main challenge of the comparison arose from the low number of eligible trials in the network, coupled with variability in the definition of ADT in these trials. Given these limitations and data availability, the most robust comparison possible was performed, details of which are presented in Section B.2.15 of Document B.

A.10.4 Generalisability of trial patient populations

The patient characteristics of the TITAN and SPARTAN patients could introduce some uncertainty into the generalisability of the trial populations to the wider UK population, as they are likely to be healthier than the general population. However, during clinical validation, a group of clinicians agreed that the baseline characteristics of both trials are reflective of UK clinical practice.[66, 67]

A.10.5 Chemotherapy-ineligible patients

As noted above, a significant proportion (up to 73%) of mHSPC patients are deemed ineligible for docetaxel, with older patients being the least likely to be eligible or suitable for chemotherapy. A report prepared by Prostate Cancer UK concluded that 64% of patients in the 69 years or younger age group diagnosed with metastatic disease received chemotherapy in 2016. In stark contrast, the uptake for chemotherapy was much lower for the over 80 years age group at only 6%.

A patient's eligibility for receiving upfront chemotherapy is multi-factorial and extends beyond just contraindications to docetaxel. Chemo-ineligible patients include those who are unsuitable for chemotherapy due to age and comorbidities, location of treatment centres and ease of access to treatment. Moreover, many patients make the difficult choice to accept an earlier death rather than receive chemotherapy, by virtue of a strong preference to maintain their good quality of life, stay in work and provide for their families.

Apalutamide offers a life-extending treatment option for these patients. As a targeted novel agent, the mechanism of action for apalutamide is distinct to that of chemotherapy. Furthermore, the treatment effect of apalutamide plus ADT has been demonstrated consistently across all pre-specified subgroups (See B.2.17 of Document B). Moreover, clinicians have stated that they would be comfortable to prescribe apalutamide to these patients, whose only treatment option is ADT alone.[67]

A.11 Overview of the economic analysis

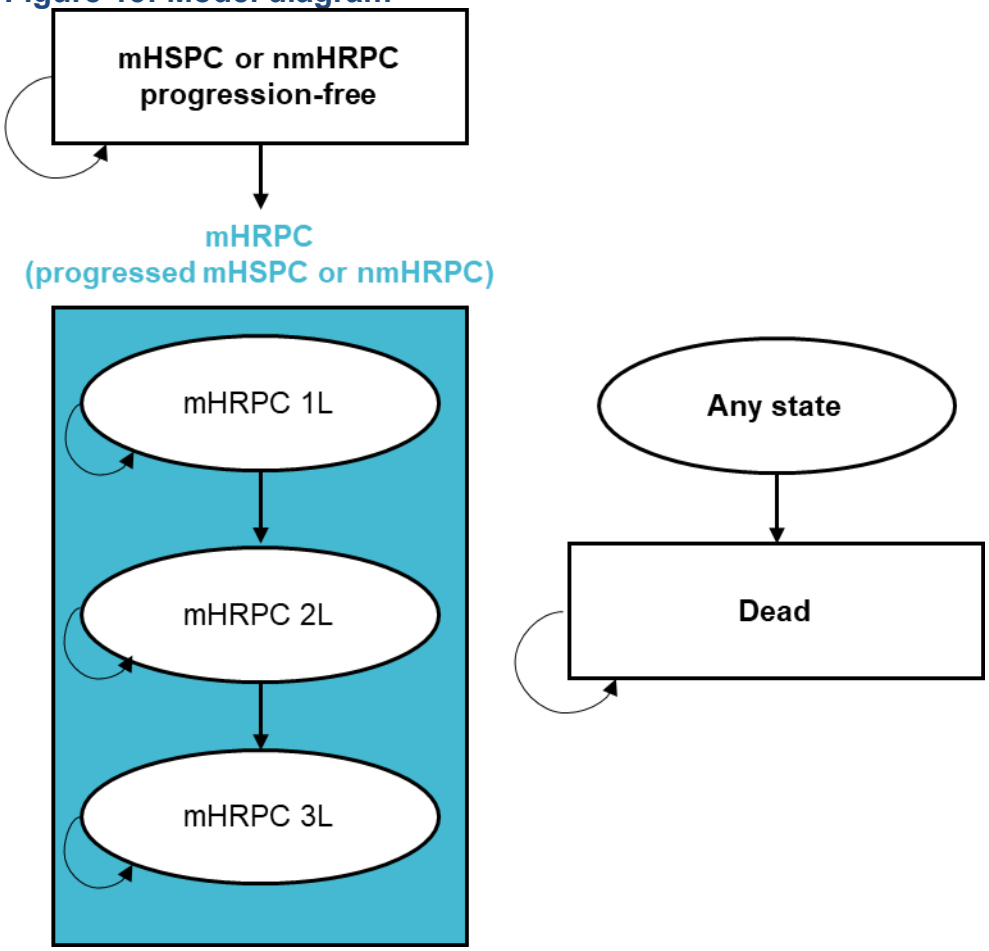
A de novo economic model was developed in Microsoft Excel® to evaluate the cost effectiveness of apalutamide plus ADT in adult men with high-risk nmHRPC and in adult men with mHSPC. The model adopted a partitioned survival analysis approach

with five mutually exclusive health states. The model structure was identical across the two indications and was informed by the disease pathway and how treatment with apalutamide may impact this, the nature of the data available to inform the analysis, committee feedback from previous NICE submissions in prostate cancer and guidance from NICE DSU TSD 19.

The model has three overarching health states of 'progression-free', 'progressed' and 'death'. The 'progressed' health state is further broken down into treatment health states, as depicted in Figure 13. Transitions through the three overarching health states are driven by progression-free survival (MFS for SPARTAN and rPFS for TITAN), and OS data from SPARTAN and TITAN. Patients within the progression-free health state could be on or off treatment as determined by time to treatment discontinuation (TTD) data. PFS2 data from SPARTAN and TITAN are used to model transitions from the 'progression-free' health state to the first of the treatment states ('mHRPC 1L') within the 'progressed' health state. Thereafter, transitions between subsequent 'progressed' treatment states ('mHRPC 2L' and 'mHRPC 3L') are driven by mean health state durations derived from NICE technology appraisal (TA) 387.[68]

The impact of subsequent treatment was modelled as accurately as possible by using PFS2 data to capture the efficacy of subsequent therapy post-apalutamide. As discussed in Section A.10 , where possible, PFS2 and OS data were adjusted to remove the confounding effect of receiving two or more novel therapies and to increase generalisability of the trial data to UK clinical practice.

Figure 13: Model diagram



Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; mHRPC, metastatic hormone-relapsed prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; nmHRPC, non-metastatic hormone-relapsed prostate cancer.

A.12 Incorporating clinical evidence into the model

A.12.1 Clinical inputs

Not all patients in the SPARTAN and TITAN trial have been followed up until disease progression and/or death; therefore, it was necessary to extrapolate TTD, PFS, PFS2 and OS over a lifetime horizon. A number of factors were considered when conducting the survival analysis:

- Proportional hazards: Two approaches for the extrapolation of PFS, PFS2 and OS were considered: 1. fitting independent models to each treatment arm, and 2. fitting a dependent model in which ADT was used as a reference curve with apalutamide plus ADT as a covariate
- Novel therapy adjustment: Analyses were conducted in which PFS2 and OS data used in the model were adjusted to reflect the one novel therapy commissioning policy in UK clinical practice. For nmHRPC, the adjusted analyses demonstrated a small impact on survival outcomes in the expected direction (reduced treatment effect for apalutamide plus ADT versus ADT). For mHSPC, however, adjustment

failed to demonstrate any significant impact on survival outcomes. Therefore, adjusted data were used for nmHRPC and unadjusted data were used for mHSPC

- Informed fits: Informed fits analyses following the methods outlined by Pennington et al. (2018)[69], where historical survival data are used to inform the survival extrapolations, was explored for both indications to reduce uncertainty in the long-term survival projections for ADT alone. For nmHRPC, a limited amount of historical ADT OS data were available and did not have longer follow-up than SPARTAN. The informed fits approach was therefore not applied. For mHSPC, however, a significant amount of historical ADT OS data that provided longer follow-up than TITAN were available from the literature. The informed fits approach was therefore adopted in the base-case analysis

In accordance with the NICE DSU TSD 14 guidance on survival analyses[70], a range of standard parametric distributions (exponential, Weibull, log-logistic, log-normal, Gompertz, and generalised gamma) were explored for the extrapolation of the PFS, PFS2, OS and TTD Kaplan–Meier data from the TITAN and SPARTAN trials.

The suitability of independent versus dependent curve fitting approaches and each of the parametric distributions were assessed using the following criteria:

- Inspection of the log-cumulative hazard plot to determine which parametric models might be suitable (supported by Schoenfeld plots / the Schoenfeld test)
- Visual inspection to assess the fit of the model to the Kaplan–Meier curve [Appendix J.1]
- Goodness-of-fit criteria including the Akaike information criterion and the Bayesian information criterion
- Assessment of how the conditional survival probability changes over time [Appendix J.1]
- Assessment of how the assumed treatment effect changes over time [Appendix J.1]
- Clinical plausibility for both short- and long-term estimates of survival, based on clinical expert validation

To estimate PFS/PFS2/OS for docetaxel plus ADT in the mHSPC indication, hazard ratios derived from the Bayesian indirect treatment comparison for docetaxel plus ADT versus apalutamide plus ADT were applied to the selected curves for apalutamide plus ADT.

A.12.2 Health-related quality of life data

Health state utilities for the ‘progression-free’ health state were derived from HRQL data collected in the clinical trials. A statistical regression analysis was performed for each indication to estimate the health state utility values from the HRQL data. SPARTAN collected EQ-5D-3L data, the recommended scale in the NICE reference

case[71], whereas TITAN collected EQ-5D-5L data, which required mapping before its input into the statistical regression. The chosen regression models in both indications included coefficients for disease progression and Grade 3/4 AEs. For mHSPC, a scenario analysis is presented applying a utility regression analysis estimated using patient level data from the STAMPEDE trial. Full methods of the utility analyses are presented in Appendix Q.

For the later lines of treatment within the 'progressed' health state, HRQL data were informed by a previous NICE submission in the mHRPC setting (TA387), because progressed HRQL data from the clinical trials were limited. As patients moved onto subsequent lines of therapy, it was assumed that their HRQL would decline over time, in line with clinical expert opinion and assumptions made in previous prostate cancer submissions.

Disutilities associated with AEs were applied across all health states. For mHSPC and nmHRPC, the utility decrements were informed by their respective utility regression analyses, whereas for mHRPC, the utility decrements were sourced from a targeted literature review. For patients receiving docetaxel + ADT in mHSPC, the AE rates for apalutamide plus ADT from TITAN were adjusted by the odds ratio estimated for Grade 3/4 AE's from the safety NMA presented in B.2.16.4. In mHSPC, an additional utility decrement estimated from the STAMPEDE trial was applied for one year in line with the assumptions in a cost-effectiveness model presented in the Woods et al. (2018) publication to capture the significant HRQL burden for patients receiving chemotherapy.

A.12.3 Cost and healthcare resource use

A confidential PAS has been submitted and is expected to be approved prior to the first appraisal committee meeting. This arrangement provides apalutamide to NHS patients at a [redacted] discount on list price. A list price of £2,735 per pack has been approved by the Department of Health and Social Care, with the PAS subsequently reducing this price to [redacted].

Costs for drug acquisition, administration, AEs, and monitoring (scheduled and unscheduled medical resource use) were all considered; full details on costs and healthcare resource use are provided in Section B.3.5 and a summary of all cost parameters included in the model is presented in Appendix P.

A.13 Key model assumptions and inputs

Table 4: Key model assumptions and inputs

Topic	Assumption	Justification	Submission
Generalisability	Patient characteristics, efficacy and safety were derived from the SPARTAN and TITAN trials and were assumed to be representative of the nmHRPC (high-risk) and mHSPC populations in the UK.	Clinical feedback confirmed that the patients in the SPARTAN and TITAN trials were reasonably reflective of patients in UK clinical practice, including mHSPC patients ineligible or otherwise unsuitable for docetaxel. The potential impact of the one novel therapy restriction in UK clinical practice has also, where possible, been accounted for in the survival analysis.	Section B.3.2
Model structure	The partitioned survival model is a suitable model structure	This is based on the guidance set out in NICE DSU TSD 19, the data available for this submission and committee feedback from previous submissions.	Section B.3.2
	Metastasis-free survival and radiographic progression-free survival are suitable proxies for disease progression in nmHRPC and mHSPC , respectively.	This was firstly based on the findings from the clinical advisory boards and precedent from previous prostate cancer submissions.	Section B.3.2
	Docetaxel is given for a maximum of six cycles.	This is applied according to NHS commissioning policy. This is also in line with the dosing schedules used in the CHAARTED and STAMPEDE studies and reflects UK clinical practice. In GETUG-AFU 15, patients received up to 10 cycles of therapy. Therefore, the model overestimates docetaxel effectiveness relative to the cost, and thus assuming six cycles of therapy is a conservative assumption.	Section B.3.5
Utilities	Baseline utility in nmHRPC and mHSPC was assumed to be similar for patients receiving apalutamide plus ADT and ADT alone.	Baseline utility before the start of treatment was similar in the apalutamide plus ADT arm and the placebo plus ADT arm in the SPARTAN and TITAN trials.	Section B.3.4

Topic	Assumption	Justification	Submission
	Patients receiving docetaxel in mHSPC are assumed to experience a utility decrement of -0.02 over a year.	This value was estimated from the STAMPEDE trial and applied for 1 year in a cost-effectiveness model presented in the Woods et al. (2018) publication.[72]	Section B.3.4
Subsequent treatments	Post-progression survival data are reflective of outcomes in UK clinical practice.	The novel therapy analyses adjusting survival outcomes for the one novel therapy commissioning policy in UK clinical practice demonstrated that use of two or more novel agents in SPARTAN and TITAN has only a small impact on the survival data.	Section B.3.3
	Most patients will receive three or fewer lines of active treatment for mHRPC.	This assumption was validated during the clinical advisory board meeting, with clinicians stating that patients would typically receive up to two active therapies, followed by best supportive care, but some could receive a third.	Section B.3.5
	ADT is received until death.	This is reflective of UK practice, as advised by UK clinicians. It is also supported by TA404 (degarelix for treating advanced hormone-dependent prostate cancer).[73] This is a conservative assumption as patients in the apalutamide arm have longer OS than those treated with ADT alone or docetaxel plus ADT. Therefore, this assumption increases treatment costs for patients treated with apalutamide relative to patients on docetaxel plus ADT or ADT alone.	Section B.3.5

Abbreviations: ADT: androgen deprivation therapy; DSU: decision support unit; mHSPC: metastatic hormone-sensitive prostate cancer; nmHRPC: non-metastatic hormone-relapsed prostate cancer; OS: overall survival; TA, technology appraisal; TSD: technical support document.

A.14 Base case ICER (deterministic)

A confidential PAS has been submitted and is expected to be approved prior to the first 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.

The key results for both indications are presented in

Table **5** to Table 8. The results for nmHRPC, and mHSPC in patients who are docetaxel ineligible demonstrate that with the confidential PAS applied, apalutamide plus ADT can be considered as a cost-effective use of NHS resources. Additionally, the results which weight the outcomes for each treatment comparison in mHSPC by the use of each comparator therapy in UK clinical practice demonstrate that apalutamide plus ADT can be considered a cost-effective treatment across the entire indication.

Table 5: Base-case results, nmHRPC, apalutamide plus ADT vs ADT alone

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ADT alone	[redacted]	5.03	[redacted]				
Apalutamide plus ADT	[redacted]	5.70	[redacted]	[redacted]	0.67	[redacted]	Dominates

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 6: Base-case, mHSPC, fully incremental results for docetaxel eligible patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ADT alone	[redacted]	4.59	[redacted]				
Docetaxel plus ADT	[redacted]	5.50	[redacted]	[redacted]	0.91	[redacted]	£9,633
Apalutamide plus ADT	[redacted]	6.02	[redacted]	[redacted]	0.52	[redacted]	£38,983

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life year gain; QALYs: quality-adjusted life years

Table 7: Base-case results, mHSPC, docetaxel ineligible patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ADT alone	[redacted]	4.59	[redacted]				
Apalutamide plus ADT	[redacted]	6.02	[redacted]	[redacted]	1.44	[redacted]	£25,329

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 8: Base-case results, mHSPC, apalutamide plus ADT vs weighted comparator (73% ADT alone, 27% docetaxel plus ADT)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Weighted comparator	[redacted]	4.83	[redacted]				
Apalutamide plus ADT	[redacted]	6.02	[redacted]	[redacted]	1.19	[redacted]	£29,016

A.15 Probabilistic sensitivity analysis

The results for nmHRPC and mHSPC are summarized in Table 9 and Table 10. The results are also presented as cost-effectiveness planes (CEP) in Figure 14, Figure 15 and Figure 16. The results are consistent with the deterministic analysis and demonstrate that apalutamide + ADT can be considered a cost-effective treatment across both the nmHRPC and mHSPC indications.

Table 9: Probabilistic sensitivity analysis results, nmHRPC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ADT alone	[redacted]	5.040	[redacted]				
Apalutamide plus ADT	[redacted]	5.703	[redacted]	[redacted]	0.66	[redacted]	Dominates

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 10: Probabilistic sensitivity analysis results, mHSPC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ADT alone	[redacted]	4.597	[redacted]				
Docetaxel plus ADT	[redacted]	5.530	[redacted]	[redacted]	0.933	[redacted]	£6,958
Apalutamide plus ADT	[redacted]	6.033	[redacted]	[redacted]	0.503	[redacted]	£39,147

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life year gain; QALY: quality-adjusted life year.

Figure 14: Cost-effectiveness plane, nmHRPC

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Figure 15: Cost-effectiveness plane, mHSPC, apalutamide vs ADT alone

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

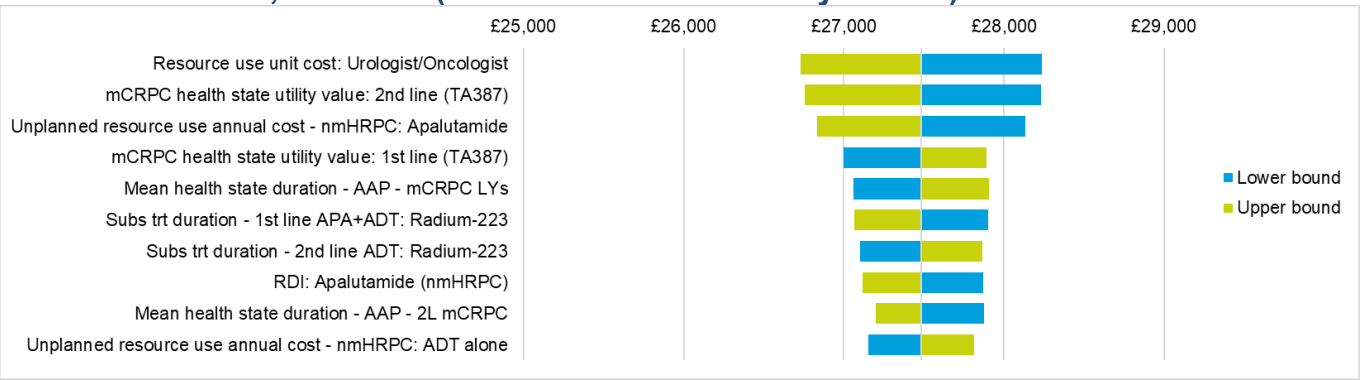
Figure 16: Cost-effectiveness plane, mHSPC, apalutamide vs docetaxel plus ADT

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

A.16 Key sensitivity and scenario analyses

For nmHRPC, Figure 17 presents a tornado diagram for apalutamide plus ADT versus ADT alone, with parameters shown in descending order of sensitivity. For mHSPC, Figure 18 and Figure 19 present results for the comparisons vs ADT alone and docetaxel plus ADT. Given the presence of negative ICER values for some of the results, incremental net monetary benefit figures are presented instead of ICERs to ensure the results are clearer to interpret. These results demonstrate that the model is relatively insensitive to the majority of parameters.

Figure 17: Results of one-way sensitivity analysis: apalutamide plus ADT versus ADT alone, nmHRPC (incremental net monetary benefit)

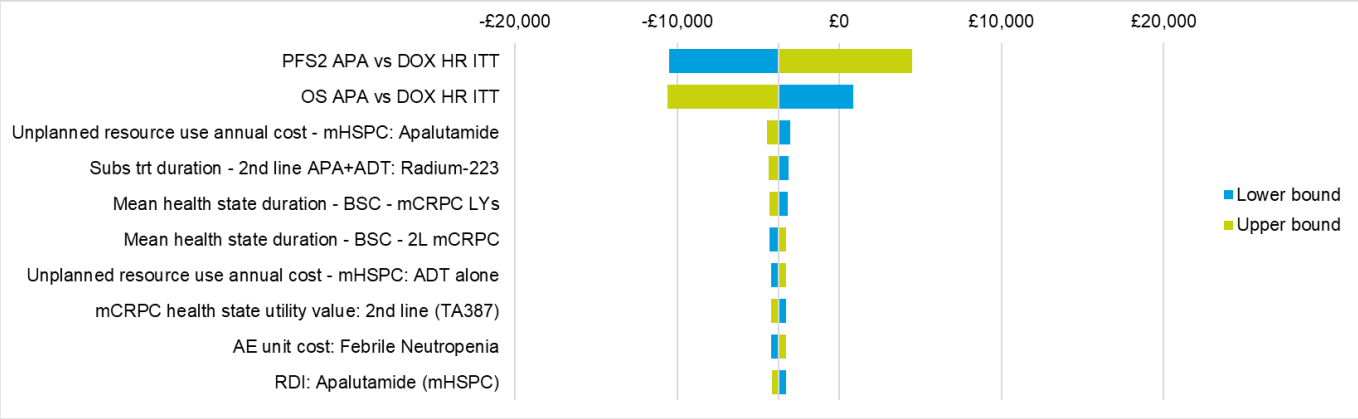


Abbreviations: AAP: abiraterone; ADT: androgen deprivation therapy; APA: apalutamide; mCRPC: metastatic castration resistant prostate cancer a.k.a metastatic hormone relapsed prostate cancer; nmHRPC: non- hormone relapsed prostate cancer; RDI: relative dosing intensity.

Figure 18: Results of one-way sensitivity analysis: apalutamide plus ADT versus ADT alone, mHSPC (incremental net monetary benefit)

Abbreviations: AAP: abiraterone; ADT: androgen deprivation therapy; APA: apalutamide; BSC: best supportive care; mCRPC: metastatic castration resistant prostate cancer a.k.a metastatic hormone relapsed prostate cancer; mHSPC: metastatic hormone sensitive prostate cancer; RDI: relative dosing intensity.

Figure 19: Results of one-way sensitivity analysis: apalutamide plus ADT versus Docetaxel plus ADT, mHSPC (incremental net monetary benefit)



Abbreviations: ADT: androgen deprivation therapy; AE: adverse events; APA: apalutamide; DOX: docetaxel; ITT: intention to treat; HR: hazard ratio; LY: life year; mCRPC: metastatic castration resistant prostate cancer a.k.a metastatic hormone relapsed prostate cancer; mHSPC: metastatic hormone sensitive prostate cancer; OS: overall survival; PFS2: second progression-free survival; RDI: relative dosing intensity.

The scenarios explored in the model are presented in Table 11 for nmHRPC and Table 12 and Table 13 for mHSPC

Table 11: Key scenario analysis results, nmHRPC

Model assumption	Base case	Scenario	ICER
Base case			Dominates
Adjustment for one novel therapy rule	Adjusted SPARTAN data	Unadjusted SPARTAN data	Dominates
Survival extrapolation for MFS	Weibull	Log-logistic	£2,147
		Log-normal	£2,602
Survival extrapolation for PFS2	Weibull	Log-logistic	Dominates
		Log-normal	Dominates
		Generalized gamma	Dominates
Survival extrapolation for OS	Weibull	Generalized gamma	Dominates
Split of first-line and second/third-line mHRPC	Estimate with PFS2	Estimate with health state durations from TA387	Dominates
Additional treatment waning	No waning	Waning between 10-15 years	Dominates
Subsequent therapy market shares	mHSPC advisory board	SPARTAN trial market shares	£28,095
		nmHRPC advisory board	Dominates

Abbreviations: ADT: androgen deprivation therapy; AE: adverse event; BSC: best supportive care; ICER: incremental cost-effectiveness ratio; mHRPC: metastatic hormone-relapsed prostate cancer; OS: overall survival; rPFS: radiographic progression-free survival.

Table 12: Key scenario analysis results, mHSPC, versus ADT alone

Model assumption	Base case	Scenario	ICER
Base case			**£25,329**
Survival extrapolation for rPFS	Weibull	Exponential	£39,187
		Log-logistic	£37,984
		Log-normal	£40,355
Survival extrapolation for OS	Weibull	Log-normal	£21,445
		Log-logistic	£23,655
		Generalized gamma	£23,329
		Gompertz	£27,884
OS curve fitting approach	Informed fits	Unstratified curves	£29,087
Split of first-line and second/third-line mHRPC	Estimate with PFS2	Estimate with health state durations from TA387	£28,216
Additional treatment waning	No waning	Waning between 10 and 15 years	£25,926
Subsequent therapy market shares	mHSPC advisory board	TITAN trial market shares	£56,896
		nmHRPC advisory board	£13,973

Abbreviations: ADT: androgen deprivation therapy; AE: adverse event; BSC: best supportive care; ICER: incremental cost-effectiveness ratio; mHRPC: metastatic hormone-relapsed prostate cancer; OS: overall survival; rPFS: radiographic progression-free survival.

Table 13: Scenario analysis results, mHSPC, versus docetaxel

Model assumption	Base case	Scenario	ICER
Base case			**£38,983**
Survival extrapolation for rPFS	Weibull	Exponential	£68,613
		Log-logistic	£60,977
		Log-normal	£67,313
Survival extrapolation for OS	Weibull	Log-normal	£26,745
		Log-logistic	£31,973
		Generalized gamma	£33,676
		Gompertz	£41,773
OS curve fitting approach	Informed fits	Unstratified curves	£45,101
Split of first-line and second/third-line mHRPC	Estimate with PFS2	Estimate with health state durations from TA387	£7,503
Additional treatment waning	No waning	Waning between 10 and 15 years	£40,231
Subsequent therapy market shares	mHSPC advisory board	TITAN trial market shares	£79,161
		nmHRPC advisory board	£31,311

Abbreviations: ADT: androgen deprivation therapy; AE: adverse event; BSC: best supportive care; ICER: incremental cost-effectiveness ratio; mHRPC: metastatic hormone-relapsed prostate cancer; OS: overall survival; rPFS: radiographic progression-free survival.

A.17 Innovation

Apalutamide is a next generation, novel anti-androgen receptor inhibitor that, when given in addition to ADT, provides significant clinical benefits versus placebo plus ADT in patients with high-risk nmHRPC and mHSPC. Several of the benefits of apalutamide are not captured in the cost per QALY calculations of the economic analysis and so are presented here.

Currently there are no treatment options other than ADT alone for patients with high-risk nmHRPC. Patients must wait until their disease has progressed to be eligible for active treatment.[20] If reimbursed, apalutamide offers the chance for patients to receive active treatment rather than receiving the standard of care which cannot delay time to progression or improve overall survival.

In mHSPC, some patients do have an alternative to standard of care with docetaxel. A significant group of mHSPC patients, however, are ineligible or otherwise unsuitable for docetaxel. In this regard, older patients are disproportionately disadvantaged as they are the least likely to be eligible or suitable for chemotherapy. For these patients, their treatment options are reduced to ADT alone. Furthermore, by virtue of a strong preference to maintain their good quality of life, stay in work and provide for their families, many patients make the difficult choice to accept an earlier death rather than receive chemotherapy. As with nmHRPC patients, apalutamide could be administered to these chemotherapy ineligible/unsuitable patients who would otherwise forgo treatment.

In both indications, receiving ADT alone rather than an active treatment carries a heavy psychological burden as patients know that their increasing PSA levels are linked to an increasing risk of developing mHRPC in the near future. Furthermore, this puts a burden on those who care for patients with prostate cancer. Although not captured in the cost per QALY analysis, the expected benefits of apalutamide in terms of psychological impact and caregiver burden are significant.

Apalutamide does not require concomitant administration of corticosteroids, and therefore does not require the additional monitoring associated with corticosteroid usage. The value of apalutamide to simplify disease management and reduce overall strain on NHS capacity and resources during and beyond the COVID-19 pandemic should not be underestimated and is not intrinsically captured in the cost per QALY framework.

A.18 Budget impact

Table 14: Budget impact, nmHRPC, PAS price (excluding VAT) – BIA (page 15)

	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible population for apalutamide plus ADT	1,769	1,777	1,785	1,792	1,799
Population expected to receive apalutamide plus ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of the treatment pathway without apalutamide plus ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of the treatment pathway with apalutamide plus ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	£481,768	£1,735,717	£3,753,457	£3,990,048	£2,229,642

Abbreviations: mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; nmHRPC: non-metastatic hormone-relapsed prostate cancer; PAS, patient access scheme; VAT, value added tax.

Table 15: Budget impact, mHSPC, PAS price (excluding VAT) – BIA (page 15)

	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible population for apalutamide plus ADT	9,629	9,673	9,716	9,754	9,791
Population expected to receive apalutamide plus ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of the treatment pathway without apalutamide plus ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of the treatment pathway with apalutamide plus ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	£1,356,443	£11,955,789	£27,075,141	£40,225,572	£49,252,842

Abbreviations: mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; nmHRPC: non-metastatic hormone-relapsed prostate cancer; PAS, patient access scheme; VAT, value added tax.

A.19 Interpretation and conclusions of the evidence

Patients with high-risk nmHRPC or mHSPC represent an area of high unmet need. Currently, for all patients with nmHRPC and those with mHSPC who are unsuitable for, or unwilling to receive docetaxel chemotherapy, their only option is to remain sub-optimally treated with ADT alone until the inevitable progression to mHRPC, the final and lethal disease stage in the prostate cancer pathway. Additionally, docetaxel is associated with substantial tolerability concerns and even in patients fit enough and willing to receive docetaxel there is a substantial impact on quality of life.

Indeed, the many patients choosing to accept an earlier death rather than receive treatment with docetaxel underscores the importance of this quality of life impact.

Compared with ADT alone, apalutamide plus ADT has demonstrated a statistically significant benefit on the risk of progression or death across both indications. Moreover, apalutamide has demonstrated a significant OS benefit in patients with high-risk nmHRPC and with mHSPC. Apalutamide not only delays progression and improves survival, it also delays the associated symptomatic sequelae of progression (such as pain), delays the need for cytotoxic chemotherapy and increases time spent with a good quality of life compared with standard of care.

Across both indications the results of the cost-effectiveness analysis demonstrate that treatment with apalutamide plus ADT can be considered a cost-effective use of NHS resources when the confidential PAS is applied. For the nmHRPC indication apalutamide plus ADT is cost-effective against ADT while for the mHSPC indication it can be considered to be a cost-effective therapy when considering the entire mHSPC patient population. The ICER was largely insensitive to the parameters and assumptions tested in both the OWSA and scenario analysis with the key model drivers being the survival extrapolations, subsequent therapy market shares and relative effectiveness versus docetaxel.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Apalutamide for treating prostate cancer [ID1534]

Clarification questions

September 2020

File name	Version	Contains confidential information	Date
ID1534 Clarification letter apalutamide.docx	Final	Yes	02/09/20

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Thank you for your thorough review of our company submission for apalutamide for treating prostate cancer. We are pleased to help provide clarification on the questions received, which we hope is helpful.

Section A: Clarification on effectiveness data

TITAN and SPARTAN trials

A1. Priority question: In TITAN, scans from approximately 60% of the patients were subject to independent central review to assess events of progression (CS Table 6). CS B.2.12.1 states that audit analysis of radiographic progression free survival (rPFS) based on blinded independent central review (BICR) were in favour of apalutamide plus ADT versus placebo plus ADT but no numerical data are provided. Please provide a table similar to CS Table 31 giving the rPFS results based on BICR.

Blinded independent review (BICR) of radiographic progression was conducted in a randomly selected sample consisting of approximately 60% of patients in TITAN. The result of this audit analysis was highly significant (HR [redacted]). The primary audit analysis by the (National Cancer Institute) NCI method confirmed the investigator assessment (Table 1).

Table 1: Summary of rPFS, Central Review)- stratified analysis (TITAN, Audit population)

ITT population	Apalutamide plus ADT (n = 304)	Placebo plus ADT (n = 296)
Event, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
rPFS (months)		
25th percentile (95% CI)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]
Range	[redacted]	[redacted]
6-month event-free rate (95% CI)	[redacted]	[redacted]
12-month event-free rate (95% CI)	[redacted]	[redacted]
24-month event-free rate (95% CI)	[redacted]	[redacted]
36-month event-free rate (95% CI)	[redacted]	[redacted]
p value [b]	[redacted]	
Hazard ratio (95% CI)[c]	[redacted]	

Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; ITT: intent-to-treat; NE: not estimable; rPFS: radiographic progression-free survival.
Notes: [a] censored observation. [b] p-value is from the log-rank test stratified by Gleason score at diagnosis (≤ 7 vs. > 7), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No). c Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favours active treatment
Source: TITAN CSR(1)

A2. CS sections B.2.11.6 and B.2.16.5 provide information on the adverse events of special interest in SPARTAN and TITAN respectively. Please explain why ischaemic heart disease was an adverse event of special interest in the SPARTAN trial, but not in the TITAN trial?

Ischaemic heart disease (IHD) was not part of the predefined adverse events of special interest for TITAN or SPARTAN. It was observed as a new adverse event in TITAN and included in the TITAN clinical study report for the interim analysis 1. Based on its identification in TITAN, IHD was included as an adverse event of special interest for the SPARTAN final analysis and will be reported as such in subsequent data cut(s) for TITAN.

Subsequent therapies

A3. Priority question: CS Table 16 provides the numbers of patients receiving life-prolonging subsequent therapy for prostate cancer in SPARTAN. Please clarify

whether patients could have received both docetaxel *and* cabazitaxel as subsequent therapies and if patients could only have received docetaxel *or* docetaxel followed by cabazitaxel (in accordance with the marketing authorisation for cabazitaxel)? Please explain why the number of patients receiving either of these therapies ([redacted] and [redacted] in the apalutamide plus ADT and placebo plus ADT groups respectively) is higher than the numbers shown in CS Table 18 (time to initiation of cytotoxic therapy) (n=155 and n=103 in the apalutamide plus ADT and placebo plus ADT groups respectively).

All subsequent therapies were initiated at the discretion of the investigators. In SPARTAN, a total of [redacted]patients in the apalutamide plus ADT arm and [redacted]patients in the placebo plus ADT arm received docetaxel, cabazitaxel or both as subsequent treatments. Of these, [redacted] patients ([redacted]%) in the apalutamide plus ADT arm and [redacted] patients ([redacted]) in the placebo plus ADT arm had docetaxel followed by cabazitaxel. By contrast, no patients in the apalutamide plus ADT arm and only [redacted] patient [redacted] in the placebo plus ADT arm received cabazitaxel followed by docetaxel. Therefore, [redacted] who had docetaxel *and* cabazitaxel received both treatments in the sequence consistent with the marketing authorisation for cabazitaxel.

Table 16 in document B of the submission presents all counts of life-prolonging subsequent treatments received by the trial patients regardless of *when* the treatment was received. It includes the first as well as follow-on subsequent lines of therapy, meaning that an individual patient could have more than one life prolonging subsequent treatment. As such, some patients received both docetaxel and cabazitaxel, which explains the higher counts observed in this table when compared to those displayed in Table 18 and those reported above.

Time to initiation of cytotoxic chemotherapy was defined as the time from randomisation to documentation of the first new cytotoxic chemotherapy being administered to the patient. Therefore, Table 18 only captures the first chemotherapy received by a given patient, leading to the lower reported counts (n=155 in the apalutamide plus placebo arm and n=103 in the placebo plus ADT arm) versus those reported in Table 16. Moreover, counts in Table 18 are higher than those reported above (first paragraph) as it was time to any cytotoxic agents, not just cabazitaxel and docetaxel.

A4. CS Table 18 provides data on time to initiation of cytotoxic chemotherapy (either docetaxel or cabazitaxel) in SPARTAN. Please explain whether cytotoxic chemotherapy was initiated at a particular point in the treatment pathway or whether

the timing of cytotoxic chemotherapy was dependent on particular clinical features &/or clinician judgement.

In SPARTAN, time to initiation of cytotoxic chemotherapy was defined as the time from randomization to documentation in the CRF of a new cytotoxic chemotherapy being administered to the patient.

Upon discontinuation from randomised treatment, subsequent therapy could be provided to any patient. The choice of subsequent therapy was at the investigator discretion. Therefore, the timing of initiation of cytotoxic chemotherapy was dependent on clinical judgement rather than any prescribed assessments related to SPARTAN trial design.

A5. Priority question: CS Table 32 provides the numbers of patients receiving life-prolonging subsequent therapy for prostate cancer in TITAN. In this table, 30 participants in the apalutamide plus ADT arm and 69 participants in the ADT alone arm have received docetaxel *and/or* cabazitaxel as subsequent therapies. Firstly, please clarify whether patients could have received both docetaxel *and* cabazitaxel or if they could only have received docetaxel *or* cabazitaxel. Secondly, please explain why an event in Table 33 (Time to cytotoxic chemotherapy) is higher (n=44 in the apalutamide plus ADT arm and n=100 in the placebo plus ADT group) than the numbers shown in CS Table 32 as receiving docetaxel *and/or* cabazitaxel.

In TITAN, all subsequent therapies were also initiated at the discretion of the investigators. A total of [redacted] patients in the apalutamide plus ADT arm and [redacted] patients in the placebo plus ADT arm received docetaxel, cabazitaxel or both as subsequent treatments. Of these, [redacted] patients ([redacted]) in the apalutamide plus ADT arm and [redacted] patients [redacted] in the placebo plus ADT arm had docetaxel followed by cabazitaxel. No patients in either the apalutamide plus ADT arm or the placebo plus ADT arm received cabazitaxel followed by docetaxel. Therefore, [redacted] who had docetaxel *and* cabazitaxel received both treatments in the sequence consistent with the marketing authorisation for cabazitaxel.

Janssen would like to highlight a misalignment in the subsequent therapies data presented for SPARTAN and TITAN in document B of the submission. Unlike in Table 16 (SPARTAN) where all life extending subsequent therapies were presented, Table 32 (TITAN) presented only the *first* subsequent therapies and therefore, the numbers presented are lower than those in Table 33 of document B (Time to cytotoxic chemotherapy) as not all patients received chemotherapy as a first subsequent therapy.

To align with Table 16 of document B (referred to in question A3), the total count of subsequent therapies that were considered life-prolonging in TITAN are presented in Table 2 below. 43 patients in the apalutamide plus ADT arm and 107 patients in the placebo plus ADT arm received docetaxel and/or cabazitaxel. These numbers are also different to those presented in Table 33 (Time to cytotoxic chemotherapy, (n=44 in the apalutamide plus ADT arm and n=100 in the placebo plus ADT group). This is because Table 2 includes all counts of docetaxel and cabazitaxel, including where both treatments were received by the same patient. Table 33 however, includes the first new cytotoxic chemotherapy received as subsequent therapy. Furthermore, Table 33 included other cytotoxic agents beside cabazitaxel and docetaxel (carboplatin, paclitaxel, etoposide, capecitabine, estramustine, cabazitaxel acetone, cisplatin, cyclophosphamide, gemcitabine, lobaplatin and mitoxantrone).

Table 2: Selected subsequent therapies for prostate cancer (TITAN, ITT population)

	Apalutamide plus ADT (n = 525)	**ADT alone (n = 527)**
Discontinued study treatment, n	177	284
Patients alive at treatment discontinuation, n (denominator for table below)	170	271
Patients with selected subsequent therapy for prostate cancer, n (%)	64 (37.6)	165 (60.9)
Docetaxel	37 (21.8)	89 (32.8)
Abiraterone	30 (17.6)	69 (25.5)
Enzalutamide	10 (5.9)	35 (12.9)
Cabazitaxel	6 (3.5)	18 (6.6)
Radium-223	6 (3.5)	10 (3.7)
Sipuleucel-T	2 (1.2)	6 (2.2)
Cabazitaxel acetone	0	1 (0.4)

Abbreviations: ADT: androgen deprivation therapy; ITT: intent-to-treat.
Source: TITAN CSR,[1]

A6. The CS states that “Novel therapies (abiraterone or enzalutamide) are known to offer a survival benefit in mHRPC but would not be used in patients who have already received apalutamide”. Aside from the novel drug commissioning policy, what would be the reason for novel therapies to be prohibited following apalutamide? Please confirm if this is due to cross-resistance between the drugs**.**

This statement was included in the CS based on Janssen’s understanding of the one novel agent commissioning policy that exists in England. This commissioning policy

pertains to use of novel agents in mHRPC and currently applies to abiraterone and enzalutamide. Janssen's understanding is that evidence of benefit related to the use of subsequent novel agents is required to allow re-treatment with a novel agent. At this time evidence of benefit is limited and research is ongoing to understand cross-resistance between apalutamide, abiraterone and enzalutamide.

Trial statistical methods

A7. CS B.2.12.1 states that a non-stratified log rank test was performed for OS as a sensitivity analysis in the TITAN trial. Was a non-stratified log rank test performed for OS as a sensitivity analysis in the SPARTAN trial? If so, what was the result?

Sensitivity analysis using a non-stratified log rank test was also conducted for OS in the SPARTAN trial. The results confirmed that treatment with apalutamide plus ADT significantly prolonged OS compared with placebo plus ADT ([redacted]).

Table 3: Summary of OS, non-stratified analysis SPARTAN (Final analysis; clinical cut-off date 1st of February 2020); ITT population

ITT population	Final analysis: Clinical cut-off date 1st February 2020 (OS unadjusted for crossover)	
	Apalutamide plus ADT (n = 806)	Placebo plus ADT (n = 401)
Event, n (%)	274 (34.0)	154 (38.4)
Censored, n (%)	[redacted]	[redacted]
OS (months)		
25th percentile (95% CI)	[redacted]	[redacted]
Median (95% CI)	73.86 (61.21–NE)	59.89 (52.80–NE)
75th percentile (95% CI)	[redacted]	[redacted]
Range	[redacted]	[redacted]
1-year survival rate (95% CI)	[redacted]	[redacted]
2-year survival rate (95% CI)	[redacted]	[redacted]
3-year survival rate (95% CI)	[redacted]	[redacted]
4-year survival rate (95% CI)	[redacted]	[redacted]
5-year survival rate (95% CI)	[redacted]	[redacted]
6-year survival rate (95% CI)	[redacted]	[redacted]
p value [b]	0.0193	
Hazard ratio (95% CI) [c]	0.790 (0.649, 0.963)	

Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; ITT: intent-to-treat; NE: not estimable; OS: overall survival; PSADT: prostate-specific antigen doubling time.

Notes: [a] Censored observation. [b] p-value is from a non-stratified log-rank test [c] Hazard ratio is from a non-stratified proportional hazards model with a single factor of treatment group, Hazard ratio < 1 favours active treatment

Source: SPARTAN FA CSR(2)

A8.CS B.2.13 states that 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 in the TITAN trial. Figure 36 presents the results of these subgroup analyses but the results of the interaction tests are not given. Please provide these results.

Compared to placebo plus ADT, apalutamide plus ADT demonstrated a treatment effect (that is an improvement in OS) across the majority of prespecified subgroups, except patients with prior docetaxel use (HR = 1.27) or visceral disease at baseline (HR = 0.99). As shown in Table *4*, however, interaction test results for prior

docetaxel use and visceral disease at baseline were negative. This indicates that the differential result for these subgroups are driven by small and imbalanced sample sizes, rather than differences in treatment effect in these subgroups.

Table 4: OS subgroup interaction effect (TITAN, ITT population)

	Joint Tests		
	DF	Wald Chi-square	Pr > ChiSq
Volume (high vs. low)*Treatment (Interaction Effect)	[redacted]	[redacted]	[redacted]
Age (<65 vs. >=65)*Treatment (Interaction Effect)	[redacted]	[redacted]	[redacted]
Bone metastasis only at baseline (yes vs. no)*Treatment (Interaction Effect)	[redacted]	[redacted]	[redacted]
ECOG grade (0 vs. 1)*Treatment (Interaction Effect)	[redacted]	[redacted]	[redacted]
Geographic region (NA/EU vs. other countries)*Treatment (Interaction Effect)	[redacted]	[redacted]	[redacted]
Prior docetaxel use (no vs. yes)*Treatment (Interaction Effect)	[redacted]	[redacted]	[redacted]
Presence of visceral disease (no vs. yes)*Treatment (Interaction Effect)	[redacted]	[redacted]	[redacted]
metastasis stage at initial diagnosis, (M0 vs M1)*Treatment (Interaction Effect)	[redacted]	[redacted]	[redacted]

Abbreviations: DF, degrees of freedom; ECOG, Eastern cooperative Oncology Group; ITT, intent to treat; M0, non-metastatic at diagnosis; M1, metastatic at diagnosis; OS, overall survival
Notes: Analyses were performed using cox model with treatment, subgroup factor, and treatment*subgroup factor.
Model dependent variable is OS, expressed as days from date of randomization to date of death from any cause. Subjects who do not have a death event at time of analysis are censored on the last date subject was known to have no death or lost to follow-up.
All factors included in the table are baseline factors.

A9. Priority question: The SPARTAN clinical study report and the TITAN clinical study reports do not appear to include Appendix 9 (the statistical analysis plans). Please provide these for both trials.

The statistical analysis plans for SPARTAN and TITAN have been submitted in separate documents (3 in total) alongside these responses.

Indirect treatment comparison

A10. The company refers to using unpublished individual patient data (IPD) for the STAMPEDE trial in several places in the submission (document B, Table 37, table 38, p135, p139). Please clarify:

- Which outcomes from STAMPEDE were analysed using IPD and for what reason?

The outcomes analysed in the network meta-analysis (NMA) were established at the feasibility assessment stage and selected to achieve the NMA objective; to determine the relative efficacy and safety of apalutamide plus ADT compared to docetaxel plus ADT.

From published data, only one efficacy outcome for STAMPEDE (OS) was available in a format comparable to study-level data from CHAARTED, GETUG-AFU 15 and TITAN. OS was therefore, implemented in the NMA using only the published data. However, comparable published data were not available for progression free survival (PFS), time to PSA progression (TTPSA), overall adverse events (AEs) and serious adverse events (SAEs). As such, access to individual patient data (IPD) from STAMPEDE (arm C versus arm A), metastatic population, was leveraged to inform the analyses for these outcomes. The hazard ratio (HR)/odds ratio (OR) and confidence intervals (CI) were calculated based on the IPD data and used as aggregate data in the NMA. Table 5 displays the source of data for each of the outcomes included in the NMA. Only the sources of the primary data were different, but the approach taken to implement the data in the NMA was the same for both data from published studies and unpublished IPD from STAMPEDE.

[redacted]

Table 5: Studies contributing data in the NMA for the relevant outcomes

Trial	OS		rPFS		rPFS + PFS[a]		TTPSA		AEs		SAEs	
	publication	Median follow-up (months)	publication	Median follow-up (months)	publication	Median follow-up (months)	publication	Median follow-up (months)	publication	Median follow-up (months)	publication	Median follow-up (months)
TITAN	Chi 2019/CSR	22.7	Chi 2019/CSR	22.7	Chi 2019/CSR	22.7	Chi 2019/CSR	22.7	Chi 2019/CSR	22.7	Chi 2019/CSR	22.7
CHAARTED	Sweeney 2015	28.9										
GETUG-AFU 15	Gravis 2013	50	Gravis 2016	83.9	Gravis 2016	83.9						
STAMPEDE (Arms C vs. A) metastatic	James 2016	43			STAMPEDE IPD (unpublished)	78.2	STAMPEDE IPD (unpublished)	78.2	STAMPEDE IPD (unpublished)	78.2	STAMPEDE IPD (unpublished)	78.2

Abbreviations: AE, adverse events; CSR, clinical study report; IPD, individual patient data; OS, overall survival; rPFS, radiographic progression-free survival; TPSA, time to PSA progression
Notes: [a] PFS data from STAMPEDE IPD was used to supplement rPFS data from TITAN and GETUG-AFU 15 as a sensitivity analysis for rPFS only.
Sources: Chi 2019,[3] Gravis 2013,[4] Gravis 2016,[5] James 2016,[6] Sweeney 2015,[7] TITAN CSR[1]

- How did the IPD outcomes analyses differ from the published aggregate outcomes analyses, in terms of numbers of patients included and results of the analysis.

  Published and unpublished data from the STAMPEDE trial were included in an aggregated format in the NMA for the relevant endpoints. As shown in Table 5, James et al 2016[6] provided data for OS and STAMPEDE IPD was used to derive similar data for PFS, TTPSA, AEs and SAEs. Patient numbers were identical in both James 2016 and STAMPEDE IPD.)

- If the IPD analyses included a different total number of patients from the aggregate data, please clarify whether the characteristics of the STAMPEDE trial, as presented in Table 37 (Document B), represent the aggregate data or the IPD data. If the former, please supply an updated table based on the IPD data.

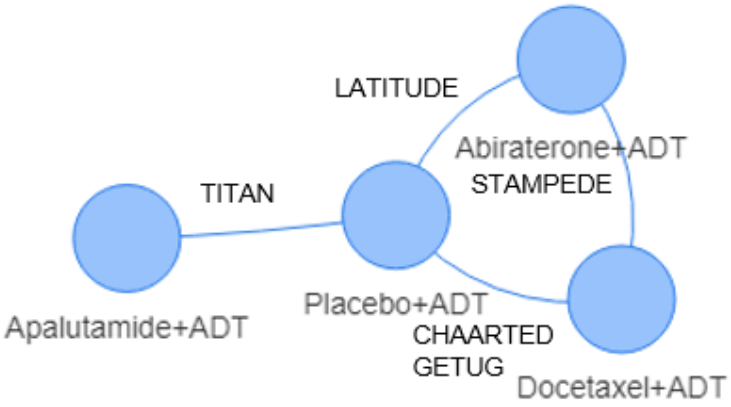
  The patients included in the STAMPEDE analyses were identical for the published data from James 2016 and the unpublished IPD. As both sets of data are based on the same trial population, the patient characteristics presented in Table 37 of Document B are also identical for James 2016 and the unpublished STAMPEDE IPD.

- Finally, please clarify whether the IPD data, as opposed to the aggregate data, was included in the NMA.

  Where STAMPEDE IPD was included, the IPD was first aggregated into study level data. This was HR and 95% CI for the time to event endpoints (PFS and TTPSA) and OR and 95% CI for the safety endpoints (AEs and SAEs). The aggregate data was then included in the NMA in the same way as the aggregate data from published sources.

A11. Please clarify why the LATITUDE trial and the abiraterone + ADT arm of the STAMPEDE trial were excluded from the NMA? The ERG believes their inclusion could have strengthened the network and provided indirect evidence for

apalutamide+ADT vs docetaxel+ADT and docetaxel+ADT vs placebo+ADT (see Figure below).



Furthermore, both studies are included in the company-sponsored NMA by Feyeraband et al (2018). Please add these studies to the network and rerun the ITC analyses, including an assessment of inconsistency for the loop in the evidence network.

Both the Feyeraband NMA and the LATITUDE trial were conducted for a different (narrower) patient population than the one specified in the decision problem for apalutamide: newly diagnosed patients with high-risk and/or high volume mHSPC. The Feyeraband NMA uses the newly diagnosed high-risk/high-volume subgroups of the CHAARTED and GETUG trials and only includes STAMPEDE in sensitivity analysis as data were not available for STAMPEDE in newly diagnosed high-risk/high-volume patients.

Available information from CHAARTED and GETUG indicate that the presence of high-risk and/or high volume mHSPC impacts absolute outcomes and may be a treatment effect modifier. Patients with low-risk disease may be less likely to benefit from the addition of docetaxel to the ADT backbone.

Adding LATITUDE to the network was therefore not considered appropriate as this would considerably increase the level of heterogeneity in the network. The abiraterone plus ADT arm of the STAMPEDE trial was excluded from the NMA as it does not add any additional evidence on relevant comparators when the LATITUDE arm is excluded.

A12. Please present evidence for or against any treatment effect modifiers. There are differences between the trials included in the NMA in terms of prior treatments, ECOG status, proportion of patients with newly diagnosed disease, high volume disease, PSA level, and Gleason score. Please confirm if these, and any other characteristics are considered effect modifiers.

A targeted review of the NMA trials publications was conducted to identify patient characteristics that were formally tested and identified as treatment effect modifiers. A summary of the findings is presented in Table 6. The factors that were shown to have an impact on OS were:

- Baseline PSA level
- Volume of disease
- Newly diagnosed versus progressed to metastatic from localised disease
- LDH
- ECOG PS score (0 versus 1)
- Number of bone lesions at baseline (<=10 versus >10)
- Presence of visceral disease (Yes versus No)

An assessment was subsequently conducted to determine the likely impact of differences in these factors across the trials on the NMA results. That is, to determine whether the differences bias the results in favour of either apalutamide plus ADT or docetaxel plus ADT as shown in Table 7.

Table 6: Summary of prognostic factors tested in the mHSPC trials

Factor	Was a formal test conducted in trial? (YES/NO)				Result if tested
	CHAARTED	GETUG-AFU 15	STAMPEDE	TITAN[a]	
PSA	NR	NR	NR	Yes	Impacts OS. Increased PSA is associated with decreased OS (TITAN CSR)
Volume of disease	Yes	Yes	Yes	Yes	OS benefit more apparent in the HV subgroup HR 0.60; 95% CI, 0.45 to 0.81; P<0.001) versus the LV subgroup HR 0.60 (95% CI, 0.32–1.13 P=0.11) (Sweeney 2015)[7] No impact on OS (GETUG-AFU, Gravis 2016)[5] No impact on OS (STAMPEDE, Clarke 2019)[8] No impact on OS (TITAN, Uemura 2019)[9]
Newly diagnosed versus progressed to metastatic from localised disease	NR	Yes	NR	Yes	No impact on OS (Bjartell 2020)[10] Impacts OS. Patients who progress to mHSPC from localised disease had a significantly longer median OS (GETUG-AFU 15, Gravis 2016)[5]
LDH	NR	NR	NR	Yes	Impacts OS. Increased LDH is associated with decreased OS
Alkaline phosphatase	NR	NR	NR	Yes	No impact on OS (TITAN CSR)
Haemoglobin	NR	NR	NR	Yes	No impact on OS (TITAN CSR)
Average Pain score at baseline	NR	NR	NR	Yes	No impact on OS (TITAN CSR)
Age	NR	NR	NR	Yes	No impact on OS (TITAN CSR)
ECOG PS (0 versus 1)	NR	NR	NR	Yes	Impacts OS. ECOG 0 is associated with better OS (TITAN CSR)

Number of bone lesions at baseline (<=10 versus >10)	NR	NR	NR	Yes	Impacts OS. A lower number of bone lesions (<=10) is associated with better OS (TITAN CSR)
Presence of visceral disease (no versus yes)	NR	NR	NR	Yes	Impacts OS. Absence of baseline disease is associated with better OS (TITAN CSR)
Receipt of localized therapy (no versus yes)	NR	NR	NR	Yes	No impact on OS (TITAN CSR)
Geographic region (NA/EU versus other countries)	NR	NR	NR	Yes	No impact on OS (TITAN CSR)
Gleason score (<=7 versus >7)	NR	NR	NR	Yes	No impact on OS (TITAN CSR)
Prior docetaxel use (no versus yes)	NR	NR	NR	Yes	No impact on OS (TITAN CSR)

Abbreviations: CSR, clinical study report; ECOG, Eastern Cooperative Group; HV, high volume; LDH, Lactate dehydrogenase; mHSPC metastatic hormone-sensitive prostate cancer; NR, not reported; OS, overall survival; PS, performance status; PSA, prostate specific antigen
Notes [a] Results from TITAN are based on a multivariate analysis of the OS data and show the prognostic characteristics that appear to influence OS at the pp<0.05 level.
Sources: Bjartell 2020,[10] Clarke 2019,[8] Gravis 2016,[5] Sweeney 2015,[7] TITAN CSR,[1] Uemura 2019[9]

Table 7: Summary of likely impact of baseline characteristics on NMA results

Prognostic factor	Trial differences	Likely direction of impact
PSA levels,	Baseline PSA levels were lower in TITAN than in any of the other trials	Against docetaxel plus ADT
Volume of disease	CHAARTED (65%) and TITAN (63%) had the highest proportion of patients with high volume disease compared to GEUG-AFU 15 (52%) and STAMPEDE (43%).	Unclear
Newly diagnosed versus progressed to metastatic from localised disease	STAMPEDE had the highest proportion of newly diagnosed patients followed by TITAN. (100% and 81 % respectively) CHAARTED (75%) and GETUG-AFU 15 (71%) had lower proportions of newly diagnosed patients	Unclear
LDH	Not reported in the docetaxel trials	Unclear
ECOG grade (0 versus 1)	There was a larger proportion of patients with a poorer performance status (ECOG/WHO PS ≥ 1) in TITAN (35.5%) than in any of the other trials.	Against apalutamide plus ADT
Number of bone lesions at baseline (<=10 versus >10)	Not reported in the docetaxel trials	Unclear
Presence of visceral disease (Yes versus No)	Proportions of patients with visceral disease at baseline comparable 14.4% in docetaxel plus ADT arm and 16.8% in ADT arm (CHAARTED) 15% in docetaxel plus ADT arm and 12% in ADT arm (GETUG) 10.7% in the apalutamide plus ADT arm and 13.7% in the ADT arm (TITAN)	Unclear

Abbreviations: ADT, androgen deprivation therapy; LDH, Lactate dehydrogenase; ECOG, Eastern Cooperative Group; mHSPC metastatic hormone-sensitive prostate cancer; NMA, network meta-analysis; OS, overall survival; PS, performance status; PSA, prostate specific antigen

The net effect of differences in baseline characteristics across the trials on the results of the NMA is likely to be minimal. These conclusions are supported by clinical expert opinion. In response to this question, a clinical expert consulted by Janssen stated that:

"None of these characteristics would influence my decision whether or not to initiate treatment with apalutamide nor do I anticipate that they would have a significant impact on the treatment effect. There may be small specific subgroups within these cohorts (for example within PSA levels there may be a subset of patients with non-androgen receptor driven disease who may have non secretory disease) but these are not representative of the typical clinical presentation."

A13. Only fixed effect results are presented. However, it appears that some random effects (RE) models were conducted: a RE prior for between-study standard deviation is mentioned in Appendix D page 212 suggesting RE was also conducted. Page 213 states RE models were fitted where feasible and presented as a sensitivity analysis but again none are presented. Please present the results of all RE models conducted. Since there was clear heterogeneity between the docetaxel=ADT vs placebo+ADT trials in OS (I^2=67.4%), was the use of an informative prior considered?

Fixed effects (FE) models were implemented for the base case as this was considered the most suitable approach given the small numbers of studies available to inform each outcome comparison which limits the ability to robustly capture the impact of heterogeneity on the results.

NMA efficacy results, random effects models

Table 8 presents the efficacy (OS, rPFS, PFS + rPFS and TTPSA) results from the random effects (RE) NMA performed as sensitivity analysis. The summary includes median HRs and 95% credible intervals and the probability that the hazard ratio for apalutamide plus ADT versus each comparator is less than one.

The results from the RE models support those generated in the base case using FE models, with point estimates for all the endpoints virtually identical for both approaches (see Table 40, Document B of the submission). Compared to the FE models, a wider variation in the 95% CrIs was observed in the RE models for all analysed efficacy endpoints as would be expected.

Whilst RE models might generally be preferred in order to be able to provide a generalisable treatment effect, in this case the number of studies informing the network is very small which means that the estimate of the between-studies variance

will have poor precision. This means we lack the information to be able to correctly apply an RE model and uncertainty will be overestimated within an RE model

Table 9 displays the surface under cumulative ranking curve (SUCRA) values for efficacy. In all the analysed endpoints, apalutamide was associated with the highest SUCRA values.

Table 8: NMA efficacy results, RE models U[0,1]

Comparison		OS	rPFS	rPFS + PFS	TTPSA
Apalutamide plus ADT vs ADT alone	HR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]
	Probability that HR is less than 1	[redacted]	[redacted]	[redacted]	[redacted]
Apalutamide plus ADT vs docetaxel plus ADT	HR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]
	Probability that HR is less than 1	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; CrI, credible interval; HR, hazard ratio; NMA, network meta-analyses; OS, overall survival; RE, random effects; rPFS, radiographic progression-free survival; TPSA, time to PSA progression.

Table 9: NMA SUCRA for efficacy, RE models U[0,1]

Comparator	OS SUCRA	rPFS SUCRA	rPFS + PFS SUCRA	TTPSA SUCRA
Apalutamide plus ADT	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel plus ADT	[redacted]	[redacted]	[redacted]	[redacted]
Placebo plus ADT	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; NMA, network meta-analyses; OS, overall survival; PFS, progression free survival; RE, random effects; rPFS, radiographic progression-free survival; SUCRA, surface under the cumulative ranking curve; TPSA, time to PSA progression.

NMA Safety results, random effects models

Table 10 presents safety results (overall AEs and SAEs) from the RE NMA for each of the treatments including the median odds ratios (ORs). The point estimates for apalutamide plus ADT versus placebo plus ADT were identical to those observed in the FE analyses for both AEs and SAEs. For the comparison of apalutamide plus ADT versus docetaxel plus ADT, the OR point estimates were lower for both overall AEs and SAEs than those observed in the FE analyses. RE ORs were associated with wider credible intervals for both safety endpoints as would be expected.

SUCRA values for safety observed with the RE models, are shown in Table 11. As in the base case, apalutamide plus ADT was associated with the highest SUCRA for both AEs and SAEs and docetaxel had the lowest values for both endpoints

Table 10: NMA safety results, RE models, U[0,1]

Comparison		Overall AEs	SAE
Apalutamide plus ADT vs ADT alone	Median OR (95% CrI)	[redacted]	[redacted]
	Probability that OR is less than 1	[redacted]	[redacted]
Apalutamide plus ADT vs Docetaxel plus ADT	OR (95% CrI)	[redacted]	[redacted]
	Probability that OR is less than 1	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; AE, adverse events; CrI, credible intervals; NMA, network meta-analyses; RE, random effects; SAE, serious adverse events.

Table 11: NMA SUCRA for safety, RE models, U[0,1]

Comparator	SUCRA for overall AEs	SUCRA for SAE
Placebo plus ADT	[redacted]	[redacted]
Apalutamide plus ADT	[redacted]	[redacted]
Docetaxel plus ADT	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; AE, adverse events; NMA, network meta-analyses; RE, random effects; SAE, serious adverse events; SUCRA, surface under the cumulative ranking curve; TPSA, time to PSA progression.

Informative prior

In the analysis presented above, U[0,1] was used as the prior distribution for the between study variability. It allows for a high degree of heterogeneity but constrains the estimate so that it cannot be extremely high in cases where there is little data to estimate the between study variability. This prior is somewhat more informative compared to the distribution suggested in the example code of the NICE DSU guidelines (U[0,5]). The U[0,5] distribution can lead to an unlikely range of heterogeneity and can cause odd results when the number of studies is low, as in our analysis.

However, in light of this question, we have rerun the analysis with a more informative prior (U[0,0.4]) and the results are presented in Table 12 and Table 13 (efficacy) and Table 14 and Table 15 (safety).

The point estimates are very similar compared to those for the FE and original RE analysis. As would be expected, the width of the CrI's are larger than those of the FE model, but smaller than those of the RE model with prior U[0,1].

Table 12: NMA efficacy results, RE models (u[0,0.4])

Comparison		OS	rPFS	rPFS + PFS	TTPSA
Apalutamide plus ADT vs ADT alone	HR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]
	Probability that HR is less than 1	[redacted]	[redacted]	[redacted]	[redacted]
Apalutamide plus ADT vs docetaxel plus ADT	HR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]
	Probability that HR is less than 1	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; CrI, credible interval; HR, hazard ratio; NMA, network meta-analyses; OS, overall survival; PFS, progression free survival; RE, random effects; rPFS, radiographic progression-free survival; TPSA, time to PSA progression.

Table 13: NMA SUCRA for efficacy, RE models (u[0,0.4])

Comparator	OS SUCRA	rPFS SUCRA	rPFS + PFS SUCRA	TTPSA SUCRA
Apalutamide plus ADT	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel plus ADT	[redacted]	[redacted]	[redacted]	[redacted]
Placebo plus ADT	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; NMA, network meta-analyses; OS, overall survival; PFS, progression free survival; RE, random effects; rPFS, radiographic progression-free survival; SUCRA, surface under the cumulative ranking curve; TPSA, time to PSA progression.

Table 14: NMA safety results, RE (u[0,0.4])

Comparison		Overall AEs	SAE
Apalutamide plus ADT vs ADT alone	Median OR (95% CrI)	[redacted]	[redacted]
	Probability that OR is less than 1	[redacted]	[redacted]
Apalutamide plus ADT vs Docetaxel plus ADT	OR (95% CrI)	[redacted]	[redacted]
	Probability that OR is less than 1	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; AE, adverse events; CrI, credible intervals; NMA, network meta-analyses; RE, random efects; SAE, serious adverse events.

Table 15: NMA SUCRA for safety, RE (u[0,0.4])

Comparator	SUCRA for overall AEs	SUCRA for SAE
Placebo plus ADT	[redacted]	[redacted]
Apalutamide plus ADT	[redacted]	[redacted]
Docetaxel plus ADT	[redacted]	[redacted]

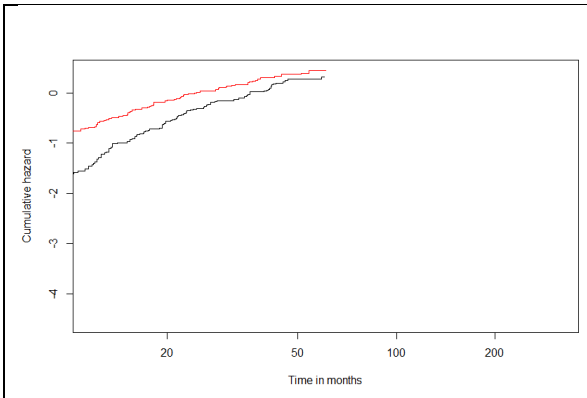
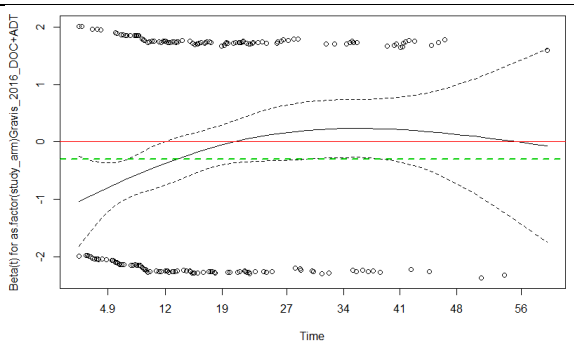
Abbreviations: ADT, androgen deprivation therapy; AE, adverse events; NMA, network meta-analyses; RE, random effects; SAE, serious adverse events; SUCRA, surface under the cumulative ranking curve; TPSA, time to PSA progression.

A14. Proportion hazards checks (Schoenfeld residuals/test, log cumulative hazards plots) for the trial period are only presented for OS in Appendix D. Please present the evidence for other time-to-event endpoints. As proportional hazards do not hold for the CHAARTED trial (OS) and GETUG trial (PFS) please consider scenario analyses excluding these studies or conduct a time-varying hazard indirect comparison.

Proportional hazards were assessed for PFS in GETUG-AFU 15 (Figure 1). They were also assessed on STAMPEDE IPD for PFS (Figure 3) and TTPSA (Figure 4) and on TITAN for rPFS (Figure 2) and TTPSA (Figure 5). The PH assumption was observed to be violated in all cases except for rPFS in TITAN.

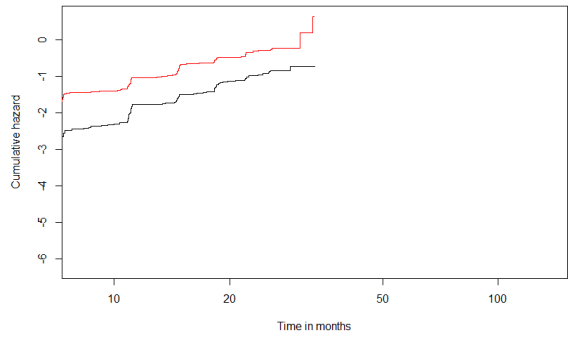
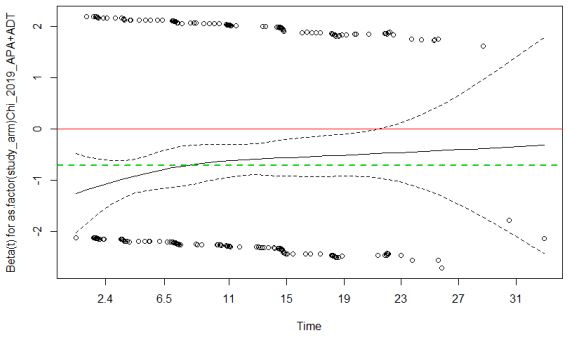
Figure 1: PFS PH assessment for GETUG-AFU 15, docetaxel plus ADT versus ADT (Gravis 2013)

Log cumulative hazard plot	Schoenfeld proportional hazard

	
	p-value=0.00523 PH assumption does not hold

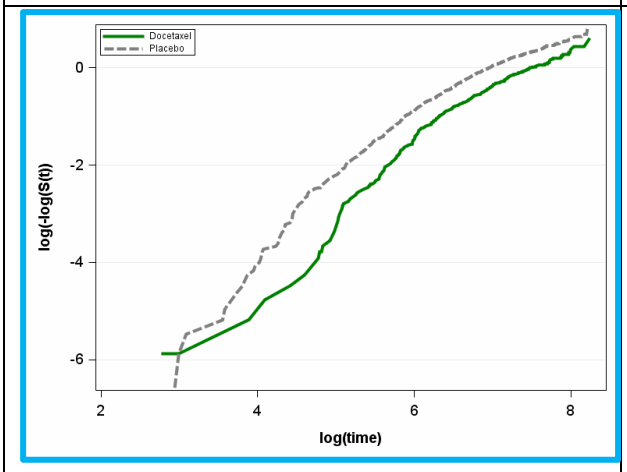
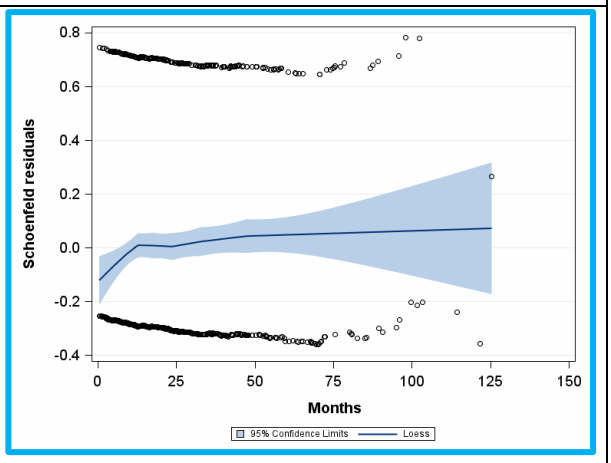
Abbreviations: ADT, androgen deprivation therapy; PH; proportional hazards; rPFS, radiographic progression free survival
Source: Gravis 2013[4]

Figure 2: rPFS PH assessment for TITAN, apalutamide plus ADT versus placebo plus ADT (Chi 2019)

Log cumulative hazard plot	Schoenfeld proportional hazard
	
	p-value= 0.0755 PH assumption holds

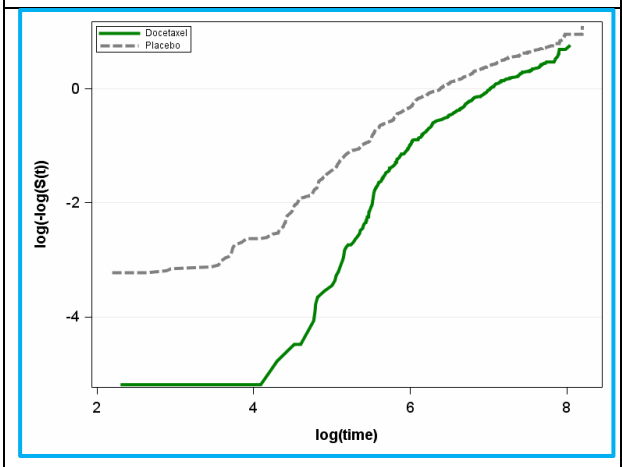
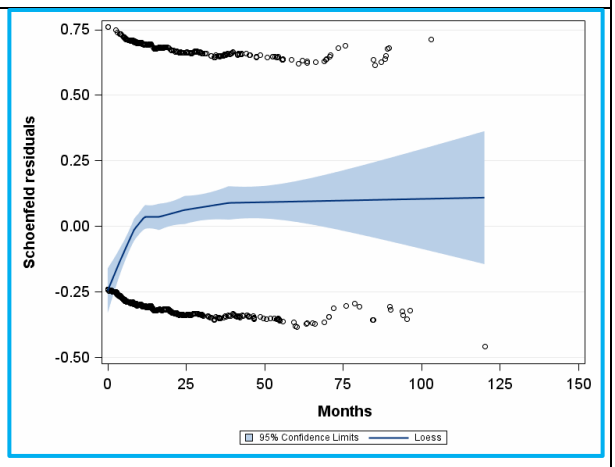
Abbreviations: ADT, androgen deprivation therapy; PH; proportional hazards; rPFS, radiographic progression free survival
Source: Chi et al 2019[3]

Figure 3: PFS PH assessment for STAMPEDE, docetaxel plus ADT versus ADT (unpublished IPD)

Log cumulative hazard plot	Schoenfeld proportional hazard
	
	[redacted]

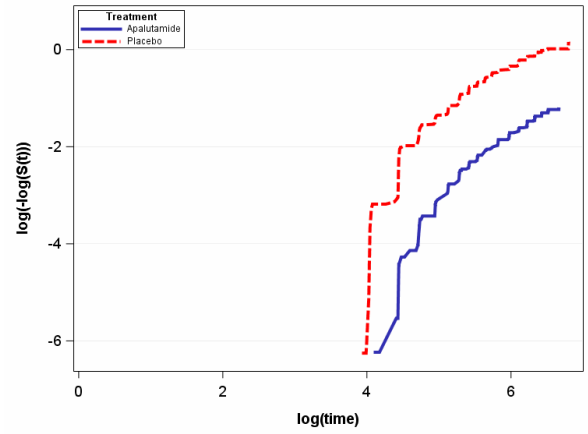
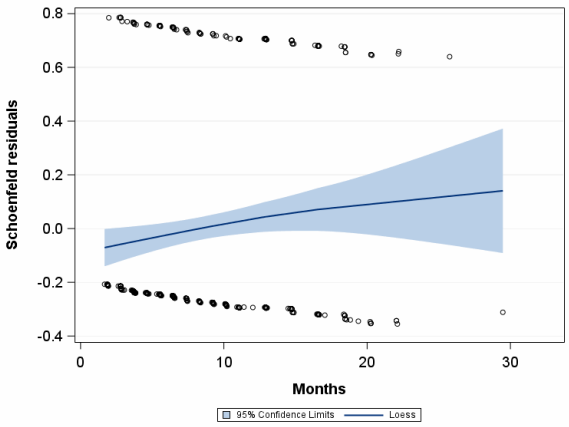
Abbreviations: ADT, androgen deprivation therapy; IPD, individual patient data; PFS, progression free survival; PH; proportional hazards;
Source: Unpublished IPD

Figure 4: TTPSA PH assessment for STAMPEDE, docetaxel plus ADT versus ADT (unpublished IPD)

Log cumulative hazard plot	Schoenfeld proportional hazard
	
	[redacted]

Abbreviations: ADT, androgen deprivation therapy; IPD, individual patient data; PH; proportional hazards; TTPSA, time to PSA progression
Source: Unpublished IPD

Figure 5: TTPSA PH assessments for TITAN, apalutamide plus ADT versus placebo plus ADT

Log cumulative hazard plot	Schoenfeld proportional hazard
	
	[redacted]

Abbreviations: ADT, androgen deprivation therapy; PH; proportional hazards, TTPSA, time to PSA progression
Source: TITAN CSR

Scenario analyses for NMA

Janssen would like to highlight that the PH assumption was satisfied for all four studies included in the base case NMA for OS. (see Figure 5 of the document B appendices). Only the later datacut from CHAARTED was observed to violate the PH assumption, Kyriakopoulos et al 2018[11] and this was only included in the sensitivity analysis exploring the impact of using OS data from the latest data-cut for each of the trials and not the base case.

Results of an additional sensitivity analysis entirely excluding this study are presented in Table 16. Excluding this study makes little difference to the results (HR = 0.81 for apalutamide vs docetaxel compared to 0.88 for apalutamide vs docetaxel in the base case)

Table 16: NMA OS results, scenario analysis[a]

Comparison		OS	
		FE	RE (U[0,1])
Apalutamide plus ADT vs ADT alone	HR (95% CrI)	[redacted]	[redacted]
	Probability that HR is less than 1	[redacted]	[redacted]

Apalutamide plus ADT vs docetaxel plus ADT	HR (95% CrI)	[redacted]	[redacted]
	Probability that HR is less than 1	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; CrI, credible interval; FE, fixed effects; HR, hazard ratio; NMA, network meta-analyses; OS, overall survival; RE, random effects
Notes: [a]This scenario excludes the Kyriakopoulos et al 2018[11] (CHAARTED) study as it violates the proportional hazards assumption.
OS data is derived from the latest available data cut for all trials

The PH assumption was also observed not to hold for PFS for Gravis 2013 (GETUG-AFU 15). In the submission, this publication did not provide data for rPFS either in the base case or the sensitivity analysis. The PH analysis was conducted as a proxy for the rPFS data in Gravis 2016, upon which the NMA was based as there was no published KM curves available for the latter publication.

Results following exclusion of the Gravis 2016 from the rPFS + PFS sensitivity NMA are presented in Table 17. The results are not different to those from the original analysis for apalutamide plus ADT versus docetaxel plus ADT (HR = 0.70)

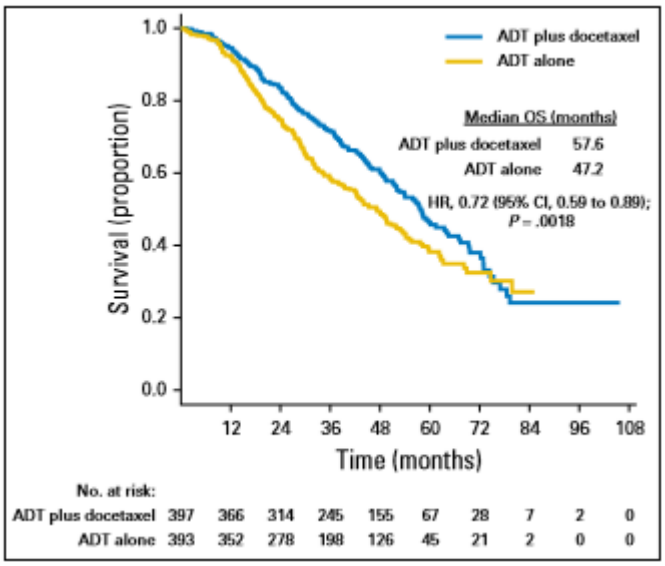
Table 17: NMA rPFS + PFS results, scenario analysis[a]

Comparison		**rPFS + PFS**	
		FE	**RE (U[0,1])**
Apalutamide plus ADT vs ADT alone	HR (95% CrI)	[redacted]	[redacted]
	Probability that HR is less than 1	[redacted]	[redacted]
Apalutamide plus ADT vs docetaxel plus ADT	HR (95% CrI)	[redacted]	[redacted]
	Probability that HR is less than 1	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; CrI, credible interval; FE, fixed effects; HR, hazard ratio; NMA, network meta-analyses; RE, random effects; PFS, progression free survival; RE, random effects; rPFS, radiographic progression-free survival;
Notes: [a]This scenario excludes Gravis 2016[5] (GETUG-AFU 15) study

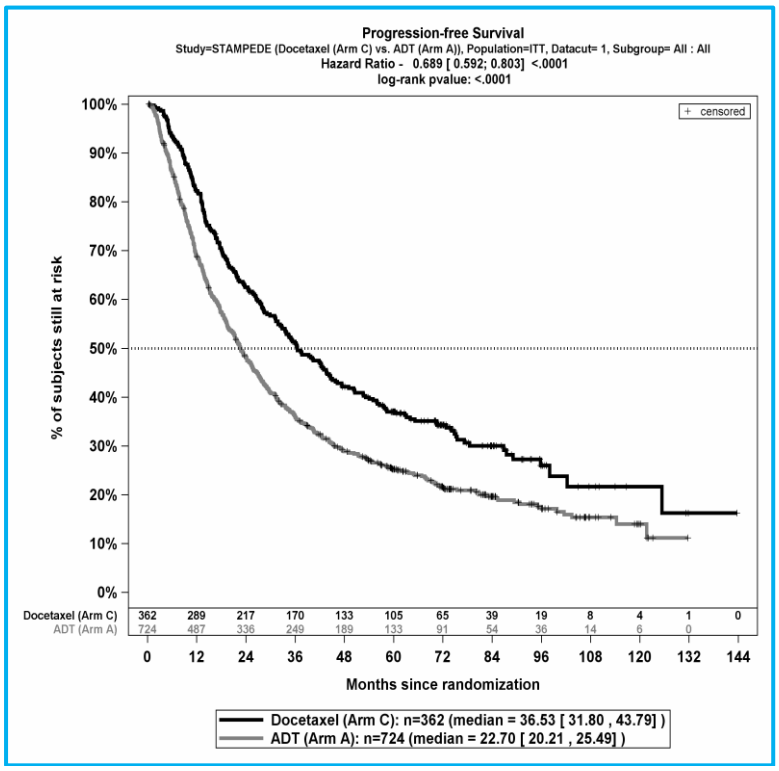
For both OS and PFS the violation of proportional hazards appears to be caused by issues with overlapping KMs at the very start of the analysis and the docetaxel plus ADT and ADT alone curves converging towards the end of the datasets (Figure 6 and Figure 7). This means that assuming proportional hazards biases the assessment of long-term effectiveness in favour of docetaxel plus ADT and therefore assuming proportional hazards represents a conservative analysis within the NMA

Figure 6: OS KM plot for CHAARTED ITT, population (Docetaxel plus ADT versus ADT alone)



Abbreviations: ADT, androgen deprivation therapy; ITT, intent to treat; KM, Kaplan Meier; OS, overall survival
Source: Kyriakopoulos et al 2018[11]

Figure 7: PFS KM plot for STAMPEDE, metastatic subgroup (Arm C [docetaxel plus ADT] versus Arm A [ADT alone]).



Abbreviations: ADT, androgen deprivation therapy; IPD, individual patient data; KM, Kaplan Meier; PFS, progression-free survival
Source: Constructed from unpublished STAMPEDE IPD

A scenario analysis including a time-varying hazard indirect comparison was not conducted. This was because there is limited data to do this robustly and the

scenario analysis excluding these studies and presented in this section achieves the goal of demonstrating the impact on the results.

A15. Please provide the WinBUGS code and accompanying study-level input data for OS and PFS used in the NMA models.

The WinBugs code used for performing the efficacy NMAs (OS and rPFS) for the FE and RE models has been provided in separate documents alongside these responses.

As described in the submission, OS data derived from trial data-cuts closest to that for TITAN were utilised in the base case and those derived from the latest available data cuts for each trial were used to inform a sensitivity analysis. Moreover, whilst rPFS data available from two trials was used to inform the base case NMA for progression free survival, a sensitivity analysis was also conducted where PFS data from a third trial were added to supplement the rPFS data.

The study level input data (HRs and 95% CI) used to conduct the NMAs for OS and rPFS are presented in Table 18 (base case analysis) and Table 19 (sensitivity analysis).

Table 18: OS and rPFS study-level input data used in the NMA base case

			OS			rPFS		
Trial	**Treatment**	**Comparator**	**Publication**	**Trial follow-up (months)**	**HR [95% CI]**	**Publication**	**Trial follow-up (months)**	**HR [95% CI]**
TITAN	Apalutamide pus ADT	Placebo plus ADT	Chi K, 2019/CSR	22.7	0.671 [0.507; 0.890]	Chi K, 2019/CSR	22.7	0.484 [0.391; 0.600]
CHAARTED	Docetaxel plus ADT	Placebo plus ADT	Sweeney C, 2015	28.9	0.610 [0.470; 0.800]	-	-	-
GETUG-AFU 15	Docetaxel plus ADT	Placebo plus ADT	Gravis G, 2013	50	1.010 [0.750; 1.360]	Gravis G, 2016	83.9	0.690 [0.550; 0.870]
STAMPEDE (arm C vs Arm A)	Docetaxel plus ADT	Placebo plus ADT	James N, 2016	43	0.760 [0.620; 0.920]	-	-	-

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; OS, overall survival; NMA, network meta-analysis; rPFS, radiographic progression free survival

Table 19: OS and rPFS study-level input data used in the NMA sensitivity analysis

			OS			rPFS + PFS		
Trial	**Treatment**	**Comparator**	**Publication**	**Trial follow-up (months)**	**HR [95% CI]**	**Publication**	**Trial follow-up (months)**	**HR [95% CI]**
TITAN	Apalutamide pus ADT	Placebo plus ADT	Chi K, 2019/CSR	22.7	0.671 [0.507; 0.890]	Chi K, 2019/CSR	22.7	0.484 [0.391; 0.600]
CHAARTED	Docetaxel plus ADT	Placebo plus ADT	Kyriakopoulos C, 2018	53.7	0.720 [0.590; 0.890]	-	-	-
GETUG-AFU 15	Docetaxel plus ADT	Placebo plus ADT	Gravis G, 2016	83.9	0.880 [0.680; 1.140]	Gravis G, 2016	83.9	0.690 [0.550; 0.870]
STAMPEDE (arm C vs Arm A)	Docetaxel plus ADT	Placebo plus ADT	Clarke, N, 2019	78.2	0.810 [0.690; 0.950]	STAMPEDE DATA	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; OS, overall survival; NMA, network meta-analysis; PFS, progression free survival; rPFS, radiographic progression free survival

A16. Please confirm whether the TITAN adjustments to account for subsequent treatments not available in England were included in the base case network meta-analysis (NMA). Also, were any similar adjustments made to other trials in the NMA?

Although adjustments to account for subsequent treatments not consistent with the one novel therapy policy in England were conducted on TITAN for the OS endpoint, the results were deemed implausible and counterintuitive. Following adjustment, apalutamide plus ADT was associated with either a similar or greater OS benefit than that shown in the unadjusted data HR =0.671 in the ITT analysis versus [redacted] for the methods of adjustment conducted; Table R.14 Appendix R). This occurred despite more patients in the apalutamide plus ADT arm of the trial having received more than one novel androgen receptor inhibitor therapy than in the placebo plus ADT arm. Therefore, the unadjusted OS result were considered more appropriate for use within the NMA.

Moreover, Janssen does not have access to IPD for all other studies included in the OS NMA (CHAARTED and GETUG) which precluded the prospect of consistently adjusting for subsequent therapies violating the one novel therapy rule in these trials. As such, to retain comparability across the studies and to avoid the confounding effect that would be introduced by using adjusted OS data from two trials and unadjusted data from the others, the unadjusted data from all four trials were implemented within the NMA.

A17. Appendix R page 844 states “overall survival in both trial arms and especially in the active arm may have been improved by novel therapy which could not have been available to these patients in the UK setting”. Please explain the rationale behind this statement, and the use of “especially” with respect to the active arm which suggests an impact on relative treatment effects. Please confirm the number of people who had treatments which are not available in the UK in the apalutamide and ADT arms of both SPARTAN and TITAN.

According to the one novel therapy rule in UK practice, patients receiving apalutamide plus ADT arm are not expected to be permitted to receive any subsequent novel treatment (abiraterone or enzalutamide), as apalutamide is also considered as a novel treatment for prostate therapy, while patients receiving ADT alone would be allowed to have abiraterone or enzalutamide as a subsequent therapy. As a consequence, a greater number of patients in the apalutamide arm do not adhere to this one-novel therapy rule, in both trials, SPARTAN and TITAN. Therefore, assuming that patients have additional survival benefit from the subsequent novel treatments, it was hypothesised that the survival estimate in the apalutamide arm as observed in the trial would be positively impacted more by “not-

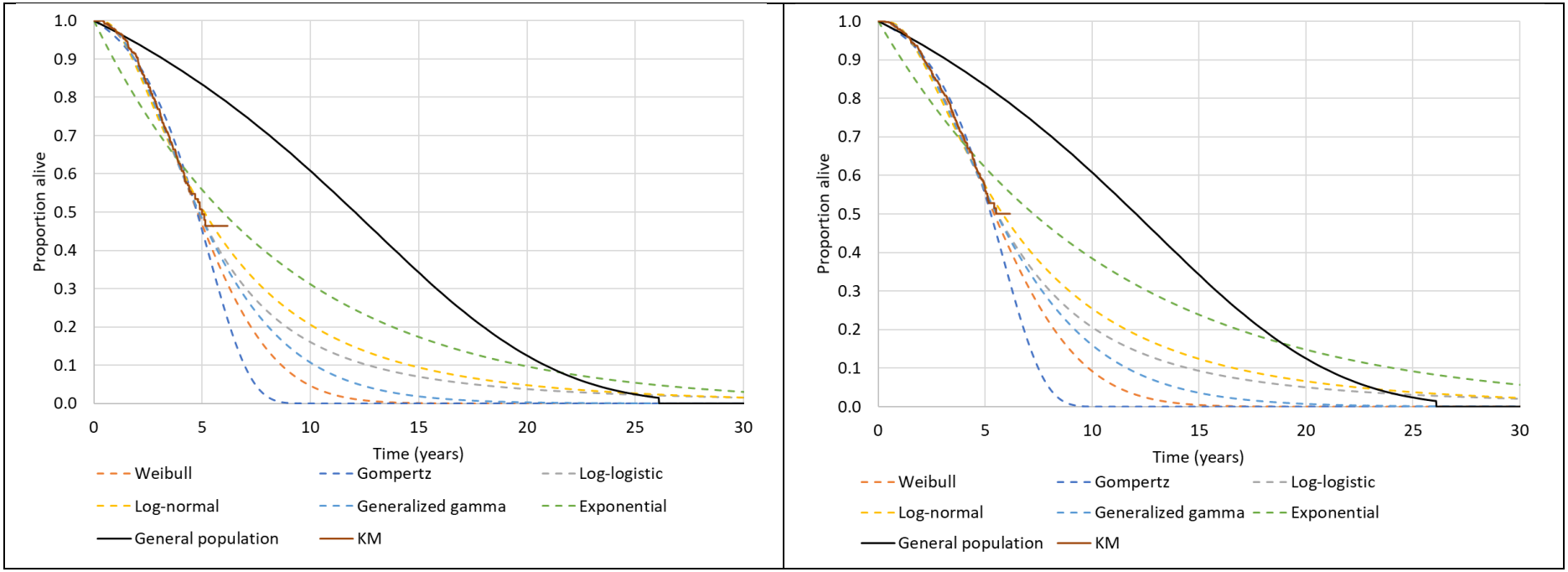
allowed" subsequent novel therapy exposure, hence the phrase "especially in the active arm".

Section B: Clarification on cost-effectiveness data

B1. The OS Kaplan Meier (KM) data for ADT in nmHRPC are different in the model (in KM! worksheet) to that in CS Table 14 for ≥3 years. Please clarify whether the model or CS is correct.

The company submission includes the correct KM data. The KM data for ADT in nmHRPC included in the model is not the correct data and has now been updated, but this has no impact on the calculations in the model. An updated version of Figure 52 from the CS is presented in Figure 8.

Figure 8: Fitted parametric models (adjusted OS, SPARTAN): ADT alone (left) and apalutamide plus ADT (right)

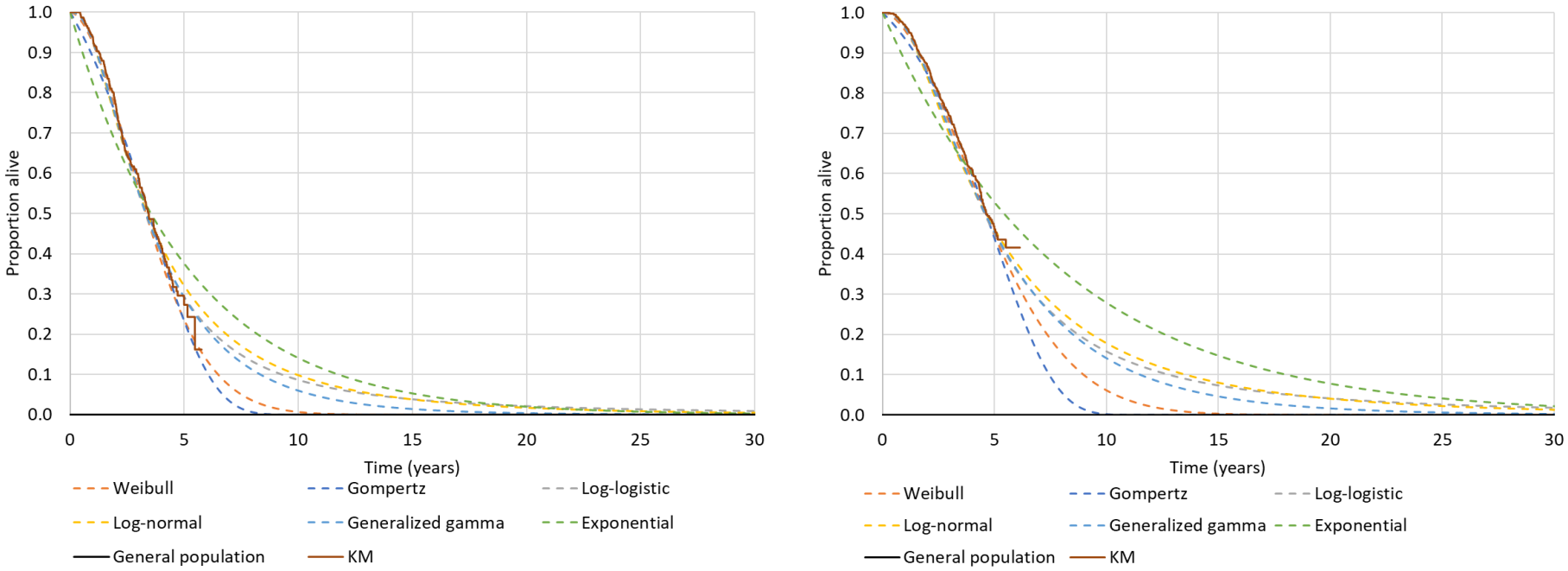


Abbreviations: ADT: androgen deprivation therapy; APA: apalutamide; OS: overall survival.

B2. The PFS2 KM data for ADT in nmHRPC are different in the model (in KM! worksheet) to that in CS Table 15. CS Table 15 appears to be same as the adjusted KM data. Please confirm the columns for adjusted and unadjusted PFS2 KM data are incorrectly labelled.

The company submission includes the correct KM data. The KM data for ADT in nmHRPC included in the model is not the correct data and has now been updated, but this has no impact on the calculations in the model. An updated version of Figure 47 from the CS is presented in Figure 9.

Figure 9: Fitted parametric models (Adjusted PFS2; SPARTAN) ADT alone (left) and apalutamide plus ADT (right)



Abbreviations: ADT: androgen deprivation therapy; APA: apalutamide; PFS2: secondary progression-free survival.

B3. Priority question: Please explain how the health state duration is estimated for mHRPC 1L, 2L and 3L in the model and provide sources of data and the data values. These durations appear not to be adjusted according to the treatments received in that treatment line. Please explain the rationale for this.

In the base case the total time patients spend in the 1L mHRPC health states is determined by the area between the PFS and PFS2 curves, and the total time patients spend in the 2L and 3L mHRPC health states is determined by the area between the PFS2 and OS curves. Therefore, the mean health state durations are simply used to split patients between the 2L and 3L health states, given there is insufficient follow-up to model the movement between these states using data from SPARTAN and TITAN. In scenario analysis the durations are used to allocate patients between the 1L, 2L and 3L mHRPC health states. The PFS2 curve is used in the base-case analysis given this provides more relevant data as it is sourced from the primary trials.

The mean durations taken from literature are applied simply to calculate proportions of time spent in each of the mHRPC states and do not dictate the time spent in mHRPC. The full methods for how these mean health state durations are used to calculate transition probabilities to move people through the mHRPC health states are reported in Section B.3.3.7.2 of the company submission.

The time spent in each of the mHRPC health states impacts the post-progression utility value that is assigned to patients, and the cost of subsequent treatments that are taken continuously until disease progression (abiraterone and enzalutamide). The time spent in each state does not influence the costs of subsequent therapies that are given for a fixed number of cycles (docetaxel, cabazitaxel and Radium-223), as these are applied as one off costs to incident patients as they enter each health state.

The mean health state durations in the base case analysis are sourced from NICE TA387 (abiraterone for treating mHRPC before chemotherapy is indicated) and are presented in Table 68 of the company submission. The unredacted table is presented below in Table 20. In this submission the health states were split into three phases: pre-docetaxel, on-docetaxel and post-docetaxel. As the submission utilised a patient-level simulation modelling approach, the duration on best supportive care in each phase is split between the time before the next phase and the time before death.

Table 20: Mean health state durations from TA387

Table 68: Summary of proportion of patients and respective duration in each treatment phase

Treatment phase	AAP		BSC (PP)	
	% in each treatment phase[a]	Mean duration (years)	% in each treatment phase[a]	Mean duration (years)
Pre-docetaxel				
1st-line active treatment	[redacted]	[redacted]	[redacted]	[redacted]
BSC (pre-docetaxel)	[redacted]	[redacted]	[redacted]	[redacted]
BSC (before death)	[redacted]	[redacted]	[redacted]	[redacted]
On-docetaxel				
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
BSC (post-docetaxel)	[redacted]	[redacted]	[redacted]	[redacted]
BSC (before death)	[redacted]	[redacted]	[redacted]	[redacted]
Post-docetaxel				
Post-docetaxel active treatment[b]	[redacted]	[redacted]	[redacted]	[redacted]
BSC (before death)	[redacted]	[redacted]	[redacted]	[redacted]

*Percentage (among the total starting population) who reach each 'state' in the treatment pathway.
[b]AAP arm: BSC (PP post-docetaxel); BSC (PP) arm: AAP (post-docetaxel).
AAP, abiraterone acetate + prednisolone; PP, placebo + prednisolone.

In the model, the health state durations from the best supportive care arm are applied for patients who progressed following treatment with apalutamide plus ADT, and the durations from the abiraterone arm are applied for patients who progressed following treatment with ADT alone (and docetaxel plus ADT in mHSPC). This was because most patients who progress after receiving ADT alone will go on to receive subsequent abiraterone or enzalutamide, whereas patients on the apalutamide plus ADT arm will not due to the restrictions in place on use of novel therapies.

The duration applied for 2L mHRPC is calculated by adding together the durations from the "docetaxel" and "BSC (post-docetaxel)" states and the duration applied for 3L mHRPC was calculated by taking the values for the "post-docetaxel active treatment" state. In scenario analysis the duration applied for 1L mHRPC is calculated by taking the values from the "1st line active treatment" health state. In this scenario an additional health state is included in the model (1L off treatment) and the duration applied for this state is calculated by taking the value from the "BSC (pre-docetaxel)" health state. The 1L off-treatment state was only modelled in scenario analysis as PFS2 does not distinguish between patients being on or off treatment.

The durations were not adjusted according to the treatments received in each treatment line. This was a simplifying assumption and was considered reasonable given the time in each health state only determines the treatment costs for abiraterone and enzalutamide, which are two treatments that are administered until disease progression and report similar PFS outcomes in mHRPC (median of 16.5 months for abiraterone and 20.0 months for enzalutamide).[12, 13]

This approach is consistent with that presented in the addendum to the company submission for NICE ID945.[14]

B4. Please confirm that the duration of treatment in mHRPC is considered equal to PFS for 1L, 2L and 3L, or provide an explanation of how treatment durations for these health states are calculated.

As noted in the response to question B3, the only subsequent treatment costs that are determined by the time spent in each of the mHRPC health states are the treatments which are administered until disease progression (abiraterone and enzalutamide). The costs for subsequent therapies that are given for a fixed number of cycles (docetaxel, cabazitaxel and Radium-223) are applied as one-off costs to incident patients as they enter the health states.

The average number of cycles applied for each of these fixed duration treatments is consistent with the numbers applied in NICE ID945 (abiraterone for treating newly diagnosed high risk mHSPC).[15-18] The number of cycles of treatment were sourced from each of the relevant trial publications. The percentage of patients completing a full course of treatment with docetaxel was based on data from the TAX327 trial. The percentage for cabazitaxel was taken from TROPIC, while the percentage of patients assumed to receive all six injections of radium-223 was taken from the ALSYMPCA trial. The proportion of patient's completing the treatment course for each of the fixed duration treatments was used to calculate the mean time on treatment as follows:

$$= \frac{(\%\ starting\ therapy + \%\ completing\ therapy)}{2} * \text{maximum}\ length\ of\ treatment$$

As noted in the response to question B3, abiraterone and enzalutamide are two treatments that are administered until disease progression and report similar PFS outcomes in mHRPC (median of 16.5 months for abiraterone and 20.0 months for enzalutamide).[12, 13] Therefore, it was considered reasonable to apply the costs for both of these therapies based on the time spent in the mHRPC health states.

B5. Please provide, if possible, unredacted data for the mean treatment durations, reported in Table 68 (p150) of the company submission for TA387 for abiraterone Please also provide, if possible, unredacted health state utility values in TA259 and

TA387 for abiraterone. These are reported in TA259 in Table 34 of the company submission (p113) and in TA387 in Table 62 (p147)

Table 21: Unredacted version of NICE TA387 table 62

Table 68: Summary of proportion of patients and respective duration in each treatment phase

Treatment phase	AAP		BSC (PP)	
	% in each treatment phase[a]	Mean duration (years)	% in each treatment phase[a]	Mean duration (years)
Pre-docetaxel				
1st-line active treatment	[redacted]	[redacted]	[redacted]	[redacted]
BSC (pre-docetaxel)	[redacted]	[redacted]	[redacted]	[redacted]
BSC (before death)	[redacted]	[redacted]	[redacted]	[redacted]
On-docetaxel				
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
BSC (post-docetaxel)	[redacted]	[redacted]	[redacted]	[redacted]
BSC (before death)	[redacted]	[redacted]	[redacted]	[redacted]
Post-docetaxel				
Post-docetaxel active treatment[b]	[redacted]	[redacted]	[redacted]	[redacted]
BSC (before death)	[redacted]	[redacted]	[redacted]	[redacted]

*Percentage (among the total starting population) who reach each 'state' in the treatment pathway.
[b]AAP arm: BSC (PP post-docetaxel); BSC (PP) arm: AAP (post-docetaxel).
AAP, abiraterone acetate + prednisolone; PP, placebo + prednisolone.

Table 22: Unredacted version of NICE TA259 table 34

	Base case		ITT			
State	**Utility value**	**SE**	**Utility value**	**SE**	**Reference in submission**	**Justification**
Pre-progression State (base case)	0.780	0.17	0.773	0.0054	Utility analysis from COU-301-AA study (Section 6.4.3 and Appendix 15)	HRQL from COU-AA-301 was most appropriate data to use in the model, as this accurately reflected QoL in the pre-progression health state
Post-progression State	0.50	0.08	0.05	0.08	Sandblom et al (2004)	Post-progression QoL was not captured in the COU-AA-301 trial after initial progression visit. Sandblom et al., provides the most robust estimate of patient QoL in the literature.
On treatment utility gain for AAP and MP (base case)	0.046	0.0105	0.045	0.0090	Utility analysis from COU-301-AA study (Section 6.4.3 and Appendix 15)	HRQL from COU-AA-301 was most appropriate data to use in the model, as this accurately reflected the on treatment QoL experienced by subjects in the study
AE disutility (applied to MP arm only)	0.072	0.0054	0.078	0.0047	Utility analysis from COU-301-AA study (Section 6.4.3 and Appendix 15)	HRQL from COU-AA-301 was most appropriate data to use in the model, as this accurately reflected the disutility experienced by subjects when and AE occurred in the study

Treatment switching

B6. Priority question: Please provide the patient-level data and code used to adjust for novel therapy and treatment switching (CS Appendix R), including all exploratory analyses, e.g. the adjustment of the survival curves from TITAN (Appendix R.3).

The code used for these analyses has been provided in a separate document to facilitate validation of the methods used.

B7. Priority question: Please clarify whether the "adjustment for one novel therapy rule" scenario in Table 95 provides the ITT analysis (i.e. analysis without adjustment for treatment switching or one novel therapy). If not, please provide this scenario.

To clarify, this scenario provides the ITT analysis.

B8. Priority question: The CS states (Appendix R page 846): "Exploratory analyses implementing IPCW to SPARTAN data generated counter-intuitive and clinically implausible results, especially for the APA-arm shifting upwards (induced by the artificial censoring), illustrating IPCW not to be valid in this case". Please provide the results of these analyses, including the code and data used, and the relevant cost-effectiveness results.

IPCW can provide unbiased estimates of the relative treatment effect if all baseline and time-varying covariates (influencing switching in each arm and survival) are correctly specified. Reliability of IPCW therefore depends on the availability of the relevant baseline and time-varying covariates driving the treatment switching and the availability of a sufficient number of (and sufficiently similar) patients continuing on treatment to represent the censored patients. On the contrary, IPCW may become unreliable when the proportion of patients switching is high and/or switching patients may be too different from non-switching patients.

The objective in conducting the IPCW analysis is to estimate counterfactual survival curves for a trial where exposure to a second novel therapy would not have been allowed, according to UK rules. Assuming that treatment with a second novel therapy has a positive impact on outcomes, the counterfactual survival curves are expected to be below the observed survival curves, representing worse outcome (and as discussed above, especially for the active arm , as more patients were exposed to a second novel therapy). IPCW-results in the current analyses for both OS and PFS2,

however, show the opposite change, with counterfactual survival curves moving upwards, suggesting that if these patients would not have been exposed to a second novel therapy, their outcomes on OS and PFS2 would have been better. This would imply that exposure to a second novel therapy is harmful, which is not clinically plausible. These results rather illustrate that in the current case assumptions behind IPCW (related to full adjustment for selection bias induced by artificially censoring patients at time of switch to the second novel therapy) are not fulfilled : the artificial censoring (as a first step in IPCW) leaves out a high number of death events (n= 183 out of 274) and PFS2 events (n=209 out of 319) from the apalutamide ADT arm (shifting survival curves upwards), which is not compensated for by the inverse probability based reweighting process: the derived IPC weights are not able to correct for the selection bias introduced by the artificial censoring at the time of switch.

As the analyses improved the outcomes for apalutamide plus ADT relative to placebo plus ADT, which is considered implausible, the results from these analyses have not been used in the cost-effectiveness model.

B9. Priority question: Please provide a cost-effectiveness analysis based on survival estimates adjusted for treatment switching using the two-stage method.

This has not been provided, as the two-stage method is not considered to be appropriate for adjustment of either the SPARTAN or TITAN datasets.

The two-stage method (see Appendix R, Section R.1) is subject to the same limitations as the IPCW method, as it suffers from insufficient data to estimate multiple parameters and to sufficiently account for time-varying confounding. Additionally, the method requires a secondary baseline at time of switching, which should happen shortly after progression/metastasis, in order to avoid time-dependent confounding. This secondary baseline cannot be reliably defined for either SPARTAN or TITAN, as the time between progression and/or discontinuation of randomized treatment and treatment switching was long in a subset of patients in the ADT arm (see Appendix R Figures 84/85 and 92/93). Additionally, the lack of updated data for progression in the more mature SPARTAN data means that conducting a reliable analysis would be very challenging as data would be taken

from IA1 for MFS whereas OS and PFS2 data would be based on the FA set to provide the longest available follow-up.

B10. The CS states (Appendix R page 847): “To overcome the above-mentioned challenge for RPSFTM on the need to estimate multiple parameters, an alternative method is proposed[326]“. The source appears to be a conference abstract. Has this method been published in a peer-reviewed journal?

A manuscript is being prepared for publication in a peer-reviewed journal based on this analysis.

B11. Priority question: Please provide the digitised curve data and code used in the informed fits analysis (CS Appendix S).

This has been provided in a separate document.

B12. As stated in CS Appendix R.3.2, “the propensity score-based approach used to match the AA-302-population to the TITAN switching population (as applied for SPARTAN, see above) was not implemented, as impact for SPARTAN was limited, and no indication that this would be different for TITAN.“ Please provide an analysis based on the propensity score-based approach.

The RPSFTM analysis implementing the propensity-score based (reweighting approach to match the AA302 population to the TITAN switching population based on baseline characteristics) was used to estimate the survival benefit of AA. Results below show that the impact on the HR of adjusting the AA302-population to the TITAN progressed patients is marginal for both OS and PFS2. This is primarily due to the very low percentage of patients not following the UK one-novel therapy rule in both arms.

Table 23: Comparison of OS hazard ratios

Method	With PS analysis[a]	exp(ψ^{ST})	TITAN HR (95% CI)
ITT			0.671 [0.51; 0.89]
RPSFTM without recensoring	[redacted]	[redacted]	[redacted]
RPSFTM with recensoring	[redacted]	[redacted]	[redacted]
RPSFTM without recensoring	[redacted]	[redacted]	[redacted]
RPSFTM with recensoring	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; ITT: intent-to-treat; RPSFTM: rank preserving structural failure time model.
a Approach used to match the AA-302-population to the TITAN switching population for the estimation of ψ^{ST}, shrinkage factor of time on ABI/ENZA.

AA302-OS KM curves – Original and matched using ATT weights

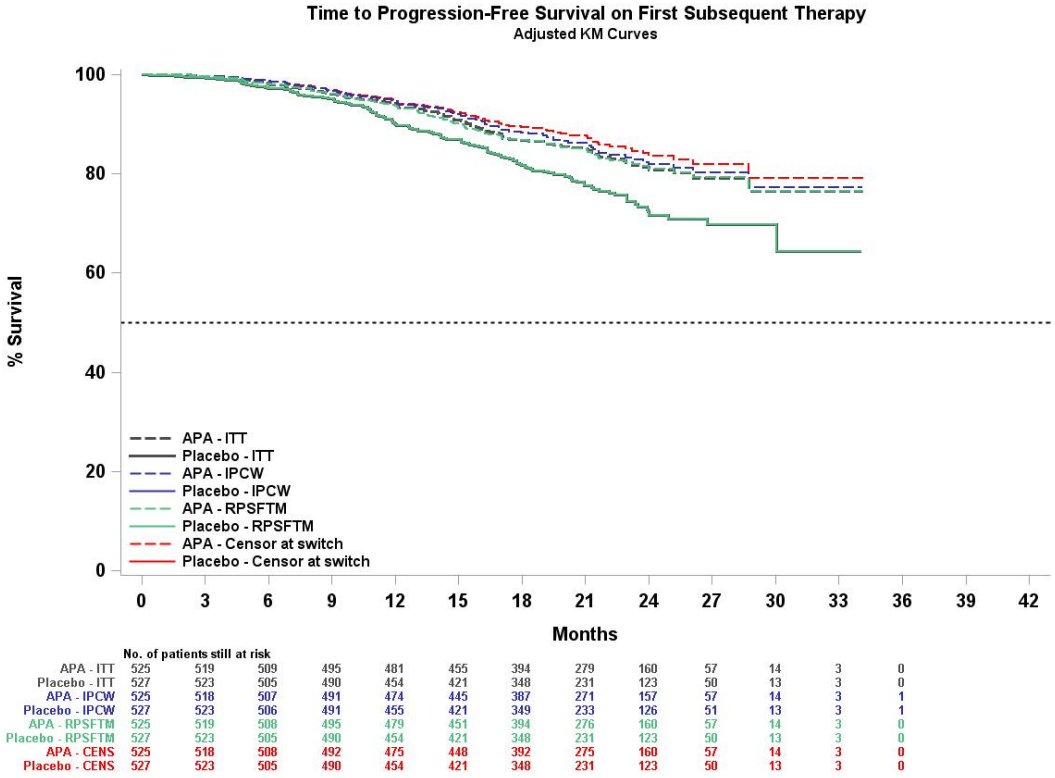
Table 24: Comparison of PFS2 hazard ratios

Method	With PS analysis[a]	exp(ψ^{ST})	TITAN HR (95% CI)
ITT			0.657 [0.50; 0.87];
RPSFTM without recensoring	[redacted]	[redacted]	[redacted]
RPSFTM with recensoring	[redacted]	[redacted]	[redacted]
RPSFTM without recensoring	[redacted]	[redacted]	[redacted]
RPSFTM with recensoring	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; ITT: intent-to-treat; RPSFTM: rank preserving structural failure time model.
a Approach used to match the AA-302-population to the TITAN switching population for the estimation of ψ^{ST}, shrinkage factor of time on ABI/ENZA.

AA302-RPFS KM curves – Original and matched using ATT weights

Figure 10: TITAN Observed and Adjusted PFS2 KM curves



Costs and resources

B13. Please explain what unscheduled resource use costs are, why these have been included and how these differ from the AE costs in the model.

The unscheduled resource use cost applied in the model was sourced from TA387 which reported a monthly cost of £93.79 (annual cost of £1,125.48). The cost was estimated from the COU-AA-302 trial which found that the main driver of resource utilisation was outpatient visits. This cost was applied in the model to capture any unscheduled inpatient or outpatient visits that occurred for reasons other than adverse events.

It is unclear whether this cost captures all unscheduled resource use including or excluding the treatment of adverse events and therefore whether there is any risk of double counting. Therefore, the results of a scenario analysis where this cost is excluded from the model (independent of other model changes outlined in other responses) are presented in Table 25 for nmHRPC and Table 26 and Table 27 for mHSPC. The results demonstrate that the exclusion of this cost has a small impact on the results.

Table 25: Results excluding unscheduled MRU costs, nmHRPC, apalutamide plus ADT vs ADT alone

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ADT alone	[redacted]	5.03	[redacted]				
Apalutamide plus ADT	[redacted]	5.70	[redacted]	[redacted]	0.67	[redacted]	Dominates

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; MRU: medical resource use; QALYs: quality-adjusted life years.

Table 26: Results excluding unscheduled MRU costs, mHSPC, fully incremental results for docetaxel eligible patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ADT alone	[redacted]	4.588	[redacted]				
Docetaxel plus ADT	[redacted]	5.501	[redacted]	[redacted]	0.913	[redacted]	£7,431
Apalutamide plus ADT	[redacted]	6.023	[redacted]	[redacted]	0.523	[redacted]	£37,924

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; MRU: medical resource use; QALYs: quality-adjusted life years.

Table 27: Results excluding unscheduled MRU costs, mHSPC, docetaxel ineligible patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ADT alone	[redacted]	4.59	[redacted]				
Apalutamide plus ADT	[redacted]	6.02	[redacted]	[redacted]	1.44	[redacted]	£23,738

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

B14. Please clarify how the adverse event unit costs used in the model have been calculated. It is unclear what inflator indices have been used to inflate the values from TA387 to those in CS Table 81. Please also clarify why the values in CS table 81 are not used in the company's model.

The cost of each adverse event was sourced from the TA387 submission when available, consistent with the approach adopted in NICE ID945. As TA387 was submitted to NICE in 2016, inflator indices were applied to adjust the costs to current prices. However, the costs applied in the model were actually taken straight from the

ID945 submission which already inflated the TA387 costs to 2018 values, and therefore inflation has been applied twice in error. The costs in the model have been replaced with those reported directly from TA387 excluding any previous adjustment for inflation to ensure that inflation is only applied once. Updated results which include this correction are presented in Table 28 for nmHRPC and Table 29 and Table 30 for mHSPC. These results demonstrate that this correction has only a minor impact on the results.

Table 28: Results with corrected adverse event costs, nmHRPC, apalutamide plus ADT vs ADT alone

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ADT alone	[redacted]	5.03	[redacted]				
Apalutamide plus ADT	[redacted]	5.70	[redacted]	[redacted]	0.67	[redacted]	Dominates

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; MRU: medical resource use; QALYs: quality-adjusted life years.

Table 29: Results with corrected adverse event costs, mHSPC, fully incremental results for docetaxel eligible patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ADT alone	[redacted]	4.588	[redacted]				
Docetaxel plus ADT	[redacted]	5.501	[redacted]	[redacted]	0.913	[redacted]	£8,786
Apalutamide plus ADT	[redacted]	6.023	[redacted]	[redacted]	0.523	[redacted]	£39,669

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; MRU: medical resource use; QALYs: quality-adjusted life years.

Table 30: Results with corrected adverse event costs, mHSPC, docetaxel ineligible patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ADT alone	[redacted]	4.59	[redacted]				
Apalutamide plus ADT	[redacted]	6.02	[redacted]	[redacted]	1.44	[redacted]	£25,303

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Utilities

B15. Priority question: Please provide a review of health state utility values for patients with mHRPC receiving 1L, 2L, 3L treatment in other relevant health technology assessments.

A summary of health state utility values for patients with mHRPC is presented in Table 31. Several of the submissions do not report complete information as some of the values have been redacted.

In the cost-effectiveness model, the progressed utility value from SPARTAN/TITAN for the nmHRPC and mHSPC indications respectively, is used as the 1L mHRPC health state utility value. Given the number of EQ-5D questionnaires completed in each trial post disease progression, there was limited data to be able to capture the decline in HRQL as patients move through the 2L and 3L mHRPC health states that has been captured in the previous NICE submissions in the mHRPC setting.

Therefore, to estimate utility values for the 2L and 3L mHRPC health states, the values reported in TA387 were used to calculate the decline in HRQL over time. The 2L and 3L mHRPC utility values reported in TA387 (0.625 and 0.5 respectively) were divided by the 1L mHRPC utility value (0.83) to estimate the decline in HRQL of moving from the 1L to 2L, and the 2L to 3L health states. These ratios were then multiplied by the progressed utility values from SPARTAN and TITAN to calculate 2L and 3L utility values that were applied in the model. This is the same approach that was adopted in NICE ID945. The values from TA387 were selected as they reported a complete set of utility values for the 1L, 2L and 3L mHRPC health states in a similar patient population. The values are also similar to those reported in TA377.

Table 31: Health state utility values from previous submissions

Appraisal	Utility values
ID945: Abiraterone	High risk mHSPC: 0.792 1L mHRPC: 0.704 2L mHRPC: 0.525 3L mHRPC: 0.420 Note the mHRPC utility values were calculated using the exact same method that is outlined in the response to B15
TA580: Enzalutamide	3L mHRPC: 0.688 End-of-life utility: 0.590 (applied for 3 months period prior to death)
TA391: Cabazitaxel	mHRPC (stable disease): 0.704-0.819 mHRPC (progressive disease): 0.6266 (until last 3 months of life which are set to 0)
TA387: Abiraterone	1L: mHRPC: 0.83 2L: mHRPC: 0.625 3L: mHRPC: 0.5
TA377: Enzalutamide	mHRPC (stable disease): 0.844 Post progression 1: 0.658 Post progression 2: 0.612 Palliative care: 0.5
TA316: Enzalutamide	mHRPC (Disutility progression): -0.085
TA259: Abiraterone	Pre-progression: 0.780 mHRPC (Post-progression): 0.5
Key: 1L, first line, 2L, second line, 3L, third line, mHRPC, metastatic hormone relapsed prostate cancer.	

B16. Please provide an overview of the utility values of the TITAN trial in the same format as in Appendix Q Table Q.3 (for SPARTAN).

Table 32: Overview of descriptive analyses results (TITAN)

	Treatment	N (obs/patients)	Mean (sd)	Q1 / Median / Q3	Min / Max
rPFS	Apalutamide	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Progression	Apalutamide	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]
rPFS without AE	Apalutamide	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]
rPFS with AE	Apalutamide	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]

Adverse events

B17. There are differences in some serious adverse event (SAE) incidence estimates in nmHRPC between the model and CS Table 26 (e.g. for fall, fracture and rash). Please clarify the reason for these discrepancies.

The values reported in CS Table 26 are accurate, whereas the values reported in the model for falls and fracture were not the precise values reported from the SPARTAN final analysis. These values have been updated in the model and the impact on the results of this correction (independent of other corrections) is presented in Table 33. However, do note that CS Table 26 only reports grade 3/4 adverse events that were reported in ≥ 5% of patients in SPARTAN and therefore as a result there are still some discrepancies between the values in the model which reflect the CSR and those in CS Table 26.

Table 33: Results with corrected adverse event rates applies, nmHRPC, apalutamide plus ADT vs ADT alone

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ADT alone	[redacted]	5.03	[redacted]				
Apalutamide plus ADT	[redacted]	5.70	[redacted]	[redacted]	0.67	[redacted]	Dominates

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

It has also been noted that there are some discrepancies between some of the rates in the model and the TITAN CSR for the mHSPC indication. Therefore, the rates for anaemia, diarrhoea and neutropenia have been updated to reflect the values reported in table TSFAE04 in the CSR. These values have been updated in the model and the impact on the results of this correction (independent of other corrections) is presented in Table 34 and Table 35.

A summary of all the adverse event rates applied in the model, including the updated values, is presented in Table 36.

Table 34: Results with corrected adverse event costs, mHSPC, fully incremental results for docetaxel eligible patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ADT alone	[redacted]	4.588	[redacted]				
Docetaxel plus ADT	[redacted]	5.501	[redacted]	[redacted]	0.913	[redacted]	£9,615
Apalutamide plus ADT	[redacted]	6.023	[redacted]	[redacted]	0.523	[redacted]	£39,077

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; MRU: medical resource use; QALYs: quality-adjusted life years.

Table 35: Results with corrected adverse event costs, mHSPC, docetaxel ineligible patients

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ADT alone	[redacted]	4.59	[redacted]				
Apalutamide plus ADT	[redacted]	6.02	[redacted]	[redacted]	1.44	[redacted]	£25,371

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

B18. Please clarify why the SAEs in mHSPC reported in CS Table 82 differ from the data in the model (anaemia, asthenia, fall, febrile neutropenia, fracture, hypertension, hypothyroidism, rash for APA+ADT arm; anaemia, asthenia fall, fracture, hypertension, rash, thrombocytopenia for ADT alone arm; and anaemia, astenhia, diarrhoea, fall, febrile neutropenia, fracture, hypothyroidism, neutropenia, rash, thrombocytopenia for the DOX+ADT arm).

The values reported in CS Table 82 are incorrect and do not reflect the true values which are reported in the model. An updated table, which includes the corrected values outlined in the response to question B17, is presented in Table 36.

Table 36: Corrected adverse events incidence rates

Adverse event	Anaemia	Asthenia	Diarrhoea	Fall	Febrile neutropenia	Fracture	Hypertension	Hypothyroidism	Neutropenia	Rash	Thrombocytopenia	Source
mHSPC												
Apalutamide plus ADT	1.7%	1.9%	[redacted]	0.8%	[redacted]	1.3%	8.4%	0.0%	[redacted]	[redacted]	[redacted]	TITAN[1]
ADT alone	3.2%	0.6%	[redacted]	0.8%	[redacted]	0.8%	9.1%	0.0%	[redacted]	[redacted]	[redacted]	TITAN[1]
Docetaxel plus ADT	2.0%	0.1%	1.0%	0.0%	7.0%	0.0%	0.0%	0.0%	32.0%	0.0%	1.0%	Gravis et al. 2013[4]
nmHRPC												
Apalutamide plus ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.0%	[redacted]	[redacted]	[redacted]	SPARTAN[2]
ADT alone	[redacted]	[redacted]	0.5%	0.8%	[redacted]	[redacted]	[redacted]	0.0%	[redacted]	0.3%	[redacted]	SPARTAN[2]
mHRPC												
Abiraterone	2.4%	0.2%	1.1%	0.0%	0.0%	0.0%	4.2%	0.0%	0.0%	0.0%	0.0%	NICE TA387
Enzalutamide	2.4%	0.2%	1.1%	0.0%	0.0%	0.0%	4.2%	0.0%	0.0%	0.0%	0.0%	Sher et al. 2012
Docetaxel	5.0%	5.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	32.0%	0.0%	1.0%	Tannock et al. 2004
Cabazitaxel	11.0%	10.0%	6.0%	0.0%	8.0%	0.0%	0.0%	0.0%	82.0%	0.0%	4.0%	De Bono et al. 2010
Radium-223	12.7%	0.8%	1.5%	0.0%	0.2%	0.0%	0.0%	0.0%	2.2%	0.0%	6.3%	Parker et al. 2013
BSC	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	

Abbreviations: ADT: androgen deprivation therapy; BSC: best supportive care; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; nmHRPC: non-metastatic hormone-relapsed prostate cancer.

Section C: Textual clarification and additional points

C1. Please insert missing digit in the upper bound of the 95%CI for PSA response rate endpoints (Table 12 of the CS) to align it with table 19.

Table 12 is reproduced below (Table 37) to include the correct digit for the upper bound of the 95% CI for PSA response rate.

Table 37: A summary of outcomes from the SPARTAN trial (ITT population – latest available data-cut)

Endpoint	Measure	Apalutamide plus ADT (n = 806)	Placebo plus ADT (n = 401)	Treatment effect (apalutamide plus ADT vs placebo plus ADT)	Data cut
MFS	Event, n (%)	[redacted]	[redacted]	HR: 0.297 95% CI: 0.244–0.362 p < 0.0001	IA1
	Median, months	40.41	15.70		
OS	Event, n (%)	274 (34.0%)	154 (38.4%)	HR: 0.784 95% CI: 0.643–0.956 p = 0.0161	FA
	Median, months	73.86	59.89		
TTM	Event, n (%)	[redacted]	[redacted]	HR: 0.279 95% CI: 0.227–0.342 p < 0.0001	IA1
	Median, months	40.51	15.70		
PFS	Event, n (%)	220 (27.3)	219 (54.6)	HR: 0.300 95% CI: 0.247–0.364 p < 0.0001	IA1
	Median, months	40.51	14.65		
Time to symptomatic progression	Event, n (%)	156 (19.4)	108 (26.9%)	HR: 0.567 95% CI: 0.443-0.725 p < 0.0001	FA
	Median, months	NE	NE		
Time to initiation of cytotoxic chemotherapy	Event, n (%)	155 (19.2%)	103 (25.7%)	HR: 0.629 95% CI: 0.489, 0.808 p = 0.0002	FA
	Median, months	NE	NE		
PFS2	Event, n (%)	319 (39.6%)	190 (47.4%)	HR: 0.565 95%CI: 0.471, 0.677 p < 0.0001	FA
	Median, months	55.56	41.17		
PSA response rate	Event, n (%)	752 (93.3)	14 (3.5)	RR: 40.090 95% CI: 20.987–76.582 p < 0.0001	IA1
Time to PSA progression	Event, n (%)	192 (23.8)	334 (83.3)	HR: 0.064 95% CI:0.052–0.080 p < 0.0001	IA1
	Median, months	NE	3.71		

Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; FA: final analysis; HR: hazard ratio; IA1: interim analysis 1; ITT: intention to treat; MFS: metastases-free survival; NE: not estimable; OS: overall survival; PFS: progression free survival; PFS2: second progression-free survival; PSA: prostate-specific antigen; RR: relative risk; TTM: time to metastasis

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Apalutamide for treating prostate cancer [ID1534]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Prostate Cancer UK
3. Job title or position	Senior Knowledge Officer
4a. Brief description of the organisation (including who funds it). How many members does it have?	Prostate Cancer UK is the UK's leading charity for men with prostate cancer and prostate problems. We support men and provide information, find answers through funding research and lead change to raise awareness and improve care. The charity is committed to ensuring the voice of people affected by prostate disease is at the heart of all we do.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	We have a policy that our total income from pharmaceutical manufacturers must be below 1%. In the 2018/19 financial year, our total income from pharmaceutical companies was less than 0.004% of our total. We regularly speak with pharmaceutical companies, particularly those with prostate cancer products, to seek funding for specific projects. This includes; £37,000 from Janssen for learning and development for our specialist nurse helpline staff and a project targeting late stage prostate cancer diagnosis; and £35,500 from Astellas to fund our improvement programme and to support the activity of our nurse helpline. In addition, we have received £20,500 each from Bayer, Sanofi, BTG and Roche towards our improvement programme.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	Patients and carers making contact with our organisation, including to our specialist nurse service; additional desk research; discussion with UK clinicians.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Men with advanced disease can present with a number of different symptoms. Evidenced symptoms for advanced prostate cancer can include[1]: • Fatigue, which can have a debilitating effect on everyday life and is linked with psychological distress. • Pain, most commonly caused by prostate cancer that has spread to the bones and which can have a significant impact on men's quality of life and mobility. • Urinary problems, this includes problems emptying the bladder, incontinence, blood in urine and kidney problems. This can have a debilitating effect on everyday life and is linked with psychological distress. • Bowel problems including constipation, diarrhoea, faecal urgency, faecal incontinence, pain, bowel obstruction and flatulence, which can cause physical and psychological distress and limit participation in daily and social activities. • Broken bones and repeated fractures caused by bone thinning that can impair mobility.

- Sexual problems, including reduced libido and difficult getting or keeping an erection. This can lead to psychological distress, challenges with intimate relationships and can affect self-esteem
- Lymphoedema, which manifests as swollen, sometimes disfigured extremities or truncal regions that can be uncomfortable, painful and cause functional impairment.
- Anaemia, caused by damage to bone marrow.
- Metastatic spinal cord compression, as cancer cells grow in or near the spine, which evidence suggests can occur in 1 to 12% of patients and requires urgent care and which, if not treated can lead to paralyses[2].
- Hypercalcaemia, caused by calcium leaking from the bones into the blood, which can result in symptoms such as nausea, vomiting and constipation.
- Eating problems that can result in malnutrition

Some or all of these symptoms can be life-changing and require a range of support services that research shows some men can struggle to access, either because of a lack of availability or because these services have a high demand. For example, The Life After Prostate Cancer Diagnosis Study (LAPCD) found that 56% of all men reported not being offered access to medications, devices, or specialist services to improve sexual function[3].· Further, access to exercise to reduce symptoms such as fatigue in men with advanced disease was found to be offered by only 17% of trusts surveyed[4].

Apalutamide is licensed for patients with metastatic hormone sensitive prostate cancer (mHSPC) and non-metastatic castrate resistant prostate cancer (nmCRPC). For the purpose of this submission, we will focus on the use of apalutamide as a treatment for men diagnosed with mHSPC. Trial data suggests that as a result of the limited sensitivity of standard imaging techniques like CT and bone scan, it is likely that men diagnosed with non-metastatic castrate resistant prostate cancer represent a population presenting with occult or low burden metastatic castrate resistant prostate cancer. In a retrospective trial of 200 patients, 55% of patients diagnosed with high-risk nmCRPC by conventional imaging received a diagnosis of metastatic prostate cancer after staging by a PSMA-PET scan[5].

This evidence, coupled with a better understanding of molecular and cellular drivers of metastatic prostate cancer, means it is plausible that the future inclusion of more sensitive modern imaging techniques such as PSMA-PET in the diagnostic pathway, the number of men diagnosed with nmCRPC will decrease, as more of these men are instead diagnosed with occult or low-burden mCRPC.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	In 2016, docetaxel chemotherapy with androgen deprivation therapy (ADT) became the standard of care for patients newly diagnosed with mHSPC. Data from Public Health England shows that a significant proportion of men newly diagnosed at this stage of the disease did not receive chemotherapy. Specifically, 63.6% of men with a new diagnosis of metastatic prostate cancer aged under 70 receive chemotherapy but this starkly decreases to 21.9% for men aged over 70 and drops further to 5.7% for men aged 80 and above. Most of these men are likely only receiving ADT and have no other life extending treatments available to them, and are missing out on the 14 extra months of life that docetaxel can provide (57.6 months vs. 44.0 months; hazard ratio 0.61; 95% confidence interval [CI], 0.47 to 0.80; P<0.001).[9] Likely, this lack of access to docetaxel is a clinical decision based on the harsh side effect profile of docetaxel, which these older men are more likely to be unable to tolerate. Side effects with docetaxel are reported mostly during treatment and in the first 6 months after treatment. Tannock et al reported that 53% of patients experienced fatigue, 65% of patients experienced alopecia, 42% experienced nausea/vomiting, 32% experienced diarrhoea and 30% experienced nail changes with docetaxel every 3 weeks[6]. Docetaxel treatment means repeatedly going into hospital, often to clinic on one day followed by chemotherapy the next day approximately every three weeks for 6 cycles of treatment. Patients are also required to self-monitor between visits, to be vigilant, recognise and to present back to hospital should any adverse reactions to treatment occur, for example, should they become febrile. There is potential for this treatment regime to be physically challenging and potentially not suitable for older men.

	However, having ADT alone means these older lose out on the potential for additional months of additional life that patients able to tolerate chemotherapy gain. They are also often living with the progressive symptoms of the disease that can limit their quality of life. This represents a health inequality that apalutamide could redress.
8. Is there an unmet need for patients with this condition?	There are currently no alternative treatments routinely available for older men with newly diagnosed mHSPC that Public Health England data shows are not receiving docetaxel + ADT. Our analysis of treatment data from 2016 drawn from the Public Health England[8] dataset, shows that 63.6% of men with a new diagnosis of metastatic prostate cancer aged under 70 receive chemotherapy. This starkly decreases to 21.9% for men aged over 70 and drops further to 5.7% for men aged 80 and above. These data reveal a cohort of men who are not receiving chemotherapy, strongly correlated with their increasing age and could therefore benefit from apalutamide. Apalutamide offers these patients the potential for additional months of life similar to what they could gain, if accessing chemotherapy. This is highlighted by the authors of the TITAN trial paper, which states that 'patients age, co-existing conditions, extent of disease and preferences may affect decisions to initiate chemotherapy such as docetaxel'. Apalutamide reduces the risk of dying from prostate cancer within 24 months by 33%[7], when compared with ADT treatment alone. The TITAN trial, which investigated the effect of apalutamide on mHSPC, showed that the overall survival percentage at 24 months was 82.4% in the apalutamide group compared with 73.5% in the placebo (ADT alone) group (hazard ratio for death, 0.67; 95% CI, 0.51 to 0.89; P = 0.005).In particular, older men over 75, who may not be able to tolerate docetaxel, had an overall survival benefit in favour of apalutamide over ADT alone (hazard ratio 0.74 (95% CI 0.41-1.35). It is also likely that this cohort of older men could tolerate apalutamide. The incidence of high-grade and serious adverse events did not differ substantially between the apalutamide and placebo groups. The most common grade 3 or 4 adverse events seen in the apalutamide group was rash. Treatment-emergent skin rash was reported by 27.1% of patients in the apalutamide group versus 8.5% in the placebo group. Grade 3 or above rashes were reported with apalutamide (6.3%) and placebo (0.6%) treatment. For lower grade events, hypothyroidism was most common. There was a small increase in fractures seen in the apalutamide group and a lesser increase in falls. Although no direct comparisons between docetaxel and

	apalutamide have been carried out, several severe (grade 3 and 4) side effects are reported for docetaxel. In the CHAARTED study[9], several grade 3 and 4 side effects were reported including 2% having grade 3 or 4 allergic reactions, grade 3 fatigue occurring in 4% of patients, and grade 3 neutropenia in 3.1% of patients and grade 4 neutropenia in 9% of patients.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Treatment with apalutamide reduces the risk of death in patients with mHSPC, compared with ADT, enabling men to have additional months of life that they are able to spend with family or friends, which they may have otherwise missed out on, if they are not able to tolerate docetaxel. In the TITAN trial, the overall survival percentage at 24 months was 82.4% in the apalutamide group and 73.5% in the placebo (ADT) group (hazard ratio for death, 0.67; 95% CI, 0.51 to 0.89; P = 0.005), resulting in a 33% lower risk of death. Treatment with apalutamide also reduces the risk of radiographic progression in men with mHSPC. In the TITAN trial, patients had a 52% lower risk of radiographic progression or death at 24 months compared. A consistent benefit was seen across all sub-groups, including patients in all age categories, disease volume, Gleason score and ECOG status. Patients are also able to maintain a good quality of life while being treated with apalutamide. In the TITAN trial, analysis of change from baseline in the functional assessment of cancer therapy - Prostate (FACT-P) score showed that health related quality of life was maintained with apalutamide.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Men experience some side effects including rash and hypothyroidism with apalutamide as detailed in section 8. However, it is likely that patients who are unable to tolerate docetaxel and have no other options for life extending treatments, would consider this a trade-off, especially if they are able maintain a good quality of life. These side effects are also arguably preferable to those experienced with docetaxel. In patients having docetaxel, 53% of patients experienced fatigue whereas 19.7% experienced fatigue with apalutamide. With docetaxel, other adverse events included 65% of patients experienced alopecia, 42% experienced nausea/vomiting, 32% experienced diarrhoea, and 30% experienced nail changes with docetaxel every 3 weeks. However, it should be noted that apalutamide is contraindicated for patients at risk of severe angina, myocardial infarction, congestive heart failure, arterial or venous thromboembolic events.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	In 2016, docetaxel chemotherapy with androgen deprivation therapy (ADT) became the standard of care for patients newly diagnosed with mHSPC cancer. Data from Public Health England shows that a significant proportion of men newly diagnosed at this stage of the disease did not receive chemotherapy. Specifically, 63.6% of men with a new diagnosis of metastatic prostate cancer aged under 70 receive chemotherapy but this starkly decreases to 21.9% for men aged over 70 and drops further to 5.7% for men aged 80 and above. Most of these men are likely only receiving ADT and have no other life extending treatments. This makes it likely that these older patients provide a cohort of men not benefiting from the current standard of care. With no other treatment options routinely available to them, these men can only receive ADT and would therefore gain additional months of life from apalutamide.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	As detailed in section 11, older patients are less likely to receive docetaxel, likely due to being unable to tolerate the side effects and therefore a large proportion of men do not have the option of the months of additional life. We consider that is unlikely to be due to patient choice, as we would not expect to see such a stark decrease with increasing age. Further, this effect parallels that of the uptake by older men of radical prostatectomy, where Prostate Cancer UK's analysis of other data in the Public Health England dataset shows a drop from 27% to 3% in the same age range. Therefore, it is unlikely that in both cases the sharp decrease in uptake by age is explained purely by patient choice, but by clinical decision over the physical burden on the patient from the treatment in question. Not making this treatment available means that older patients are unable to experience the benefit from the additional months of life of any treatment, and have no treatment options available to them, except ADT alone. This is therefore a potential equality issue and should be taken into account when

	considering apalutamide in men with mHSPC.
Other issues	
13. Are there any other issues that you would like the committee to consider?	Given that the patient sub-group most likely to benefit from this treatment only receive ADT, the appraisal should only consider ADT as the comparator.
Key messages	

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Data from Public Health England shows that a significant proportion of men newly diagnosed with mHSPC did not receive chemotherapy. Specifically, 63.6% of men with a new diagnosis of metastatic prostate cancer aged under 70 receive chemotherapy but this starkly decreases to 21.9% for men aged over 70 and drops further to 5.7% for men aged 80 and above. Most of these men are likely only receiving ADT and have no other life extending treatments available and would benefit from apalutamide.
- As there is a cohort of men only accessing ADT, apalutamide provides a clear benefit, reducing the risk of death and of radiographic progression in men with mHSPC, compared to ADT, which should be considered the comparator for the older patient population not accessing docetaxel.
- Data suggests an equivalent benefit for overall survival when compared to studies looking at docetaxel.

- Apalutamide enables patients to maintain quality of life to a much greater degree than the current standard treatment, docetaxel, with less severe side effect profile.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Apalutamide for treating prostate cancer [ID1534]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	TACKLE Prostate Cancer
3. Job title or position	Patient Representative for Tackle
4a. Brief description of the organisation (including who funds it). How many members does it have?	Tackle is a patient centred charitable organisation whose aims are to support men and their families whose lives are affected by prostate cancer. In addition we aim to represent the opinions of patients on any subject which is relevant to the diagnosis and treatment of prostate cancer. We represent 91 support groups in England and Wales and through them have 15,000 members - men and their families whose lives have been affected by prostate cancer. Tackle is a registered Charity. Income is from bequests/gifts and fundraising by members. We receive unrestricted grants from various companies in the pharmaceutical industry
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months?	Janssen: £10,000 Unrestricted Grant, January 2020 Astellas: £9,500 Unrestricted Grant, June 2020 Janssen: £10,000 Unrestricted Grant to cover Covid crisis July 2020
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO
5. How did you gather information about the experiences of patients and	Tackle gain regular feedback from our members via face to face contact at local and national meetings, from direct contact by telephone from individuals and from the questions and queries of patients on our patient helpline. We have a medical advisory board who advise when and where necessary. I do not have personal experience of being treated with Apalutamide. The clinical indications under discussion are potentially new indications for use of the drug and thus no patient has direct experience of using it at this point in their treatment pathway apart from those patients involved in clinical trials. However, I have considerable contact patients who are faced with the clinical scenarios concerned in this appraisal with

carers to include in your submission?	and understand their needs and concerns. Tackle believe that it is appropriate for me to speak on their behalf.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**Non-metastatic hormone relapsed Prostate Cancer - nmhrPCa** The term *'non-metastatic castrate resistant prostate cancer'* is unintelligible to most patients. The term *'non-metastatic hormone relapsed prostate cancer'* is perhaps more easily understood. However, the journey that many patients experience is: 1. Localised disease treated with surgery or radiotherapy 2. A subsequent rise in PSA treated successfully with hormone therapy (Androgen Deprivation Therapy - ADT) 3. A further subsequent rise in PSA as ADT fails to work. This so-called *'biochemical recurrence'* where PSA is rising rapidly (high risk patients are defined as having a PSA doubling time of less than 10 months) is frequently in patients who have few physical symptoms and where conventional scanning shows no detectable metastases. These patients will inevitably progress to the metastatic phase - often quite rapidly - when significant symptoms of bone pain or even pathological fractures will require strong analgesics and quality of life will be significantly diminished. nmhrPCa is a clinical situation where progress to identifiable metastatic disease is almost inevitable but to one where approved treatment is already available. For the patient, his family and carers it is extremely hard to understand why treatment cannot be offered earlier to potentially delay, or possibly even prevent, the onset of this spread. It can be a source of considerable psychological distress and may be of long duration until spread is identified. No patient expects 'miracles' at this stage of disease. However, treatment that can extend life with a good quality would bring enormous benefits both physiologically and psychologically to patients and their families/carers. Apalutamide would appear to offer the ability to help provide that treatment. Families & Carers often feel very impotent in helping their relatives through their journey with cancer of any sort. This can be particularly apparent in nmhrPC where the added stress of "*knowing something is*

	happening but not knowing where" can be immense. Adequate therapy at this stage with treatments which produce an acceptable side effect profile would be of immense value. The patient viewpoint is best summarised by what patients have told us: *"To be honest, to know my disease is worsening but not being able to have any treatment is unbearable. In a strange way I would feel better if you had told me I had definitely got spread - at least I would be getting some treatment now. At least I would have an end-point to relate to."* **Metastatic hormone sensitive prostate cancer - mhsPCa** Metastatic hormone sensitive prostate cancer may develop as a progression from the non-metastatic phase but can also occur in newly diagnosed men. A man newly diagnosed with high risk metastatic hormone sensitive prostate cancer (ndhrhsPCa) is given a total 'bombshell' of a diagnosis. Not only is he told he has a cancer but also the possibility that he only has a very limited life span. It is a time of deep emotional and psychological distress for all of these men, their families and carers. This is particularly true for those men who previously had no symptoms and have often been diagnosed on a routine medical examination. A significant number of these men will be relatively young and with young families. The diagnosis will undoubtedly take over the life of the patient not only immediately but often for the whole of the life he has remaining. In the TITAN trial 80% of men studied were newly diagnosed. What the patient will expect are swift and definitive treatment options. His future life will be significantly changed by not only the symptoms of his disease but also by the potential side effects of his treatments. He will know he has reduced life expectancy and will wish to have the best quality of life during that period. The possibility of extending life and increasing the time before further progression of the disease is of paramount importance. For all of these men the only further option available is chemotherapy. Not all men, particularly older men, will be able to have chemotherapy. Apalutamide would offer an acceptable alternative.

Current treatment of the condition in the NHS	
.7. What do patients or carers think of current treatments and care available on the NHS?	**Non-metastatic hormone relapsed Prostate Cancer - nmhrPCa** There is no currently approved treatment pathway for patients who have nmhrPCa. It gives great uncertainly and distress to patients. They are highly anxious to have treatment that will slow down progress of the disease. Some patients are offered 'off licence' treatments e.g. bicalutamide or dexamethasone, but the majority are offered nothing. There is no consensus of opinion as to when, if ever, such treatment should be started. Patients do not even have the ability to choose whether they wish to undergo further additional therapy or not. Their only option is to wait for the inevitable metastases to become apparent - by then it might be too late for adequate treatment. The development of metastases will have significant consequences medically, have increased cost issues to the NHS and severe impact on the quality of life of the patient. Patients with nmhrPCa invariably feel confused, anxious, depressed, hopeless and helpless. **Metastatic hormone sensitive prostate cancer - mhsPCa** Because of the very positive results from trials of the use of a combination of ADT and chemotherapy, some men with ndhrhsPCa are now offered this combination as first line therapy – although there is no actual specific licence for the use of docetaxel in this context. This has been shown to significantly increase survival time. For many men this is a very appropriate treatment option. However, recent data from the National Prostate Cancer Audit show that the uptake / use of this adjuvant therapy is not as high as it could be. For those men unable or unwilling to have chemotherapy, or those who experience considerable early side effects from chemotherapy, there is currently no alternative approved additional drug therapy that can be combined with standard ADT. Currently available drugs, Abiraterone or enzalutamide, are restricted to use once ADT is shown to be failing to control the cancer. For many patients in both clinical scenarios under appraisal, current therapy is thought to be inadequate. The need for an alternative to chemotherapy is paramount.

8. Is there an unmet need for patients with this condition?	**Non-metastatic hormone relapsed Prostate Cancer - nmhrPCa** There is no definitive clarity for either patients or clinicians as to how this clinical scenario should be managed if they are not able to have chemotherapy as an adjuvant drug. Currently the only option to patients with a rapidly rising PSA, other than just seeing their PSA continue to rise and waiting for metastases to be found, is to request more sensitive scans such as Choline PET or Ga^{68} PSMA scanning which may detect metastases earlier. These are not readily available to all patients. However, there is no NICE approved pathway to then allow treatment in this situation even if small metastases are found. Some patients may be able to have treatment (e.g. Abiraterone or Enzalutamide) on a self-funding basis, some via private health insurance but there is currently no approved access via the NHS. **Metastatic hormone sensitive prostate cancer - mhsPCa** Adjuvant therapy (i.e. Docetaxel) has been shown to delay the progression of prostate cancer, extend survival and increase quality of life for the patient, although for many patients each treatment cycle can produce significant side effects which tend to increase as treatment progresses. There are patients who are unable to have docetaxel because of age, pre-existing medical conditions or have been unable to continue Docetaxel because of adverse effects. Currently there is no other adjuvant therapy available to them. An alternative to chemotherapy in both clinical scenarios under appraisal is required. Currently a significant number of patients are not able to have optimal therapy because they are unable to have Docetaxel. This constitutes a considerable unmet need.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Slowing progression of the cancer, slowing the onset of side effects of the cancer and the extension of survival are certainly huge increases in quality of life. It allows patients time to plan the future of not only their own lives but that of those around them. This is particularly true for men who have been newly diagnosed and now have a severely limited life span. However, longevity of life on its own is not sufficient and must be associated with an acceptable quality of life. Increased time to the need the onset of bone metastases, the potential for pathological fractures and the need for opioid analgesia are secondary but

	equally important endpoints for the patient. Apalutamide has been well tolerated by men when used similarly as additional therapy. Oral administration of a therapy is much simpler than systemic delivery. Apalutamide is taken once daily by mouth. Less monitoring of the patient with blood tests etc is required that with Abiraterone and this can reduce the need for hospital vistis and consultations. Apalutamide would seem to be a very acceptable alternative to Docetaxel.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The ultimate aim for a patient is that any new/additional therapy should have the maximum therapeutic benefits but with minimal additional side effects. In common with other androgen receptor blocking drugs, Apalutamide may produce fatigue, exacerbate hypertension, hot flushes, arthralgia etc. However, patients, particularly older patients, tolerate the side effects of Apalutamide better than those produced by chemotherapy and for many can be a better drug. Unique to Apalutamide is the incidence of skin rashes, but these are said to be minor adverse events and normally only requiring topical therapy. In some patients an adjustment in dosage may be required.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The patients who will benefit the most are those who currently are unable to be given Docetaxel because of clinical contra-indications and those who are unable to tolerate the side effects produced by Docetaxel. There is currently no alternative for patients to choose should they wish not to have Docetaxel. An increase in the incidence of seizures has been reported with other similar drugs. Patients with a history of seizures were excluded from studies and such patients are not recommended to be treated with Apalutamide. Cost of therapy may be an issue and may have an additional financial burden on healthcare providers. This, however, is not the responsibility / concern of the patient. There is always concern that provision of a treatment may not always be available locally to every patient on cost grounds despite a treatment being 'approved' by regulatory bodies.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There are no obvious equality issues with regard to race, social class etc. However, it is agreed that optimal therapy for some patients will be a combination of ADT and another agent – currently the only approved adjuvant drug is Docetaxel. There are patients who, because of their age and deceased tolerance to potential side effects, are unable to have Docetaxel. When there is an equally effective alternative available and which is tolerated better by patients, it could be reasonably argued that withholding such a drug from these patients is discrimination purely because of their age and therefore this should be highlighted as a potential equality issue.
Other issues	
13. Are there any other issues that you would like the committee to consider?	This submission is written in July 2020. At the time of writing the date for the NICE Committee meeting relevant to this appraisal is 4th March 2021. There are a number of drugs currently undergoing appraisal that could be used in similar clinical indications. The outcome of those appraisals may, at a later date, potentially influence on the opinions and statements made in this current submission. The current approach to the treatment of prostate cancer could be criticised for being one that is 're-active' rather than being 'pro-active'. Except for using Docetaxel as an adjuvant medication early in the treatment of newly diagnosed metastatic prostate cancer, the treatment pathway for prostate cancer could be best described as 'serial monotherapy' - i.e. just using one drug until it fails and then adding another. Early 'multi-modal' therapy is common with other cancers. Men with prostate cancer are often now aware of such a treatment strategy and are beginning to question a treatment regime that relies of a series of single therapies only. Multi-modal therapy using radiotherapy is now increasing – the combination of brachytherapy and external beam radiotherapy is increasingly being used in selected patients – the so-called 'brachytherapy boost'. There is increasing evidence that multiple drug therapy is also effective in improving the outcomes for patients with prostate cancer but there is a great unmet need for drugs to be approved for used within the NHS in this way.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Accepted opinion is that the optimal treatment for a patient with newly-diagnosed metastatic hormone sensitive prostate cancer is a combination of ADT and Docetaxel. Patients unable to have Docetaxel for whatever reason currently have no alternative drug available to them and will therefore potentially be treated sub-optimally.
- Non-metastatic hormone resistant prostate cancer presents a major problem for patients who currently have no therapy available to them. Whilst many may not have severe perceive physiological problems at that time, they, and all those around them, all perceive considerable psychological distress.
- Currently there is no alternative drug to Docetaxel approved by NICE that can be used in any of the clinical indications under appraisal.
- Any alternative to Docetaxel must be effective in producing extension of progression free survival and overall extension of life. However, quantity of life must be combined with quality of life and secondary end-points are of significance to the patient. The side effects of that alternative must produce an acceptable balance of both.
- There is a great unmet need for adjuvant therapy that can be used alongside ADT or when ADT fails. Apalutamide appears to fulfil that role.

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

Apalutamide for treating prostate cancer

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Declared competing interests of the authors and advisors

- The authors report none.
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- Professor James reports receiving consulting fees, advisory boards and lecture fees (none >£2000) in the previous 12 months from the following companies associated with this appraisal: Astellas Pharma, AstraZeneca UK, Bayer, Janssen (NB. unrelated to apalutamide), Orion Pharma UK, and Sanofi.

Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Keith Cooper critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Irina Tikhonova critically appraised the health economic systematic review, critically appraised the economic evaluation and drafted the report; Lois Woods critically appraised the clinical effectiveness systematic review, conducted bibliographic searches, and drafted the report; Lorna Hazel critically appraised the clinical effectiveness systematic review, and drafted the report; Inês Souto Ribeiro critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Jo Picot critically appraised the clinical effectiveness systematic review, and drafted the report; David Scott critically appraised the clinical effectiveness systematic review and drafted the report; Jonathan Shepherd critically appraised the clinical effectiveness systematic review, drafted the report and is the project guarantor.

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LIST OF ABBREVIATIONS

1L	First line
2L	Second line
3L	Third line
AAP	Abiraterone
ADT	Androgen deprivation therapy
AE	Adverse event
AIC	Academic in confidence
APA	Apalutamide plus ADT
BNF	British National Formulary
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CIC	Commercial in confidence
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
DOX	Docetaxel plus ADT
DSU	Decision Support Unit
EGP	Economic Guidance Panel
EMA	European Medicines Agency
EMC	Electronic Medicines Compendium
ENZA	Enzalutamide
EPAR	European Public Assessment Report
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
EQ-VAS	EuroQol Visual Analogue Scale
ERG	Evidence Review Group
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio

Incr	Incremental
IPD	Individual patient level data
ITT	Intent to treat
KM	Kaplan Meier
LY	Life-years
LYG	Life-years gain
mCSPC	Metastatic castration sensitive prostate cancer
MFS	Metastasis-free survival
mHRPC	Metastatic hormone relapsed prostate cancer
mHSPC	Metastatic hormone sensitive prostate cancer
mITT	Modified intent to treat
MP	Mitoxantrone plus prednisolone
MRU	Medical resource use
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
nmCRPC	Non metastatic castration relapsed prostate cancer
nmHRPC	Non metastatic hormone relapsed prostate cancer
NR	Not reported
OS	Overall survival
PartSA	Partitioned survival analysis
PAS	Patient Access Scheme
PSA	Prostate specific antigen
PFS	Progression free survival
PFS2	Secondary progression free survival
PP	Prednisolone plus placebo
PSS	Personal Social Services
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
rPFS	Radiographic progression free survival
RPFSTM	Rank Preserving Structural Failure Time Model
RR	Relative risk/risk ratio
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error

SLR	Systematic literature review
SmPC	Summary of product characteristics
SPARTAN	Selective Prostate AR Targeting with ARN-509
STA	Single Technology Appraisal
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TITAN	Targeted Investigational Treatment Analysis of Novel Anti-androgen
TSD	Technical Support Document
TTD	Time to treatment discontinuation
UK	United Kingdom
US	United States
VAS	Visual analogue scale

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1 Summary of key issues

Issue number	Summary of issue	Report sections
1	Selection of methods to adjust for treatment switching in the pivotal apalutamide clinical trials	3.2.2 (Risk of bias), 3.2.4 (Trial statistical methods), 4.2.6, 4.2.7 and 4.2.8 (Treatment effectiveness extrapolation methods).
2	Clinical and cost effectiveness of apalutamide in people with mHSPC who are ineligible or unsuitable for docetaxel chemotherapy	2.3 (Critique of the company's definition of the decision problem), 3.2.6.6 (Subgroup analyses), 4.2.3 (Economic model population)
3	Extrapolation of metastatic free survival / radiographic progression free survival	4.2.7 (Treatment effectiveness and extrapolation)
4	Utility values for second and third line metastatic hormone relapsed prostate cancer (mHRPC) health states	4.2.10 (Health related quality of life)
5	Market share of subsequent therapies used metastatic hormone relapsed prostate cancer (mHRPC)	4.2.11 (Resources and costs)
6	Duration of treatment costs for adverse events associated with docetaxel	4.2.11 (Resources and costs)

Of the key issues in Table 1, there are differences between the company's preferred and the ERG's preferred assumptions for the following parameters:

- The utility values for second and third line mHRPC health states were adjusted by first line mHRPC utility in the company's base case, but were not adjusted in the ERG's preferred base case.
- The costs of treating adverse events associated with docetaxel were applied for the whole of the mHSPC health state in the company's base case, but only for six months in the ERG's preferred base case.

The assumptions related to the remaining key issues were not changed in the ERG's preferred base case.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Table 2 and Table 3 report the base case results for apalutamide in the nmHRPC and the mHSPC indications, respectively, based on the Patient Access Scheme (PAS) discount price for apalutamide. The results show that apalutamide plus ADT dominates ADT alone for nmHRPC. For mHSPC, the ICER for apalutamide plus ADT versus ADT alone is £25,329 per QALY and versus docetaxel plus ADT is £38,983 per QALY.

Table 2 Company's base case results for nmHRPC (discounted, PAS price for apalutamide)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£/QALY)
ADT alone	[redacted]	5.03	[redacted]				
Apalutamide plus ADT	[redacted]	5.70	[redacted]	[redacted]	0.67	[redacted]	Dominates

Source: reproduced from CS Table 85.
ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gain; QALYs: quality-adjusted life years.

Table 3 Company's base case fully incremental results for mHSPC (discounted, PAS price for apalutamide)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£/QALY)	ICER (£/ QALY): APA vs. ADT
ADT alone	[redacted]	4.588	[redacted]					
Docetaxel plus ADT	[redacted]	5.501	[redacted]	[redacted]	0.913	[redacted]	9,633	
Apalutamide plus ADT	[redacted]	6.023	[redacted]	[redacted]	0.523	[redacted]	38,983	25,329
Source: reproduced from CS Table 88 and CS Table 89. ADT: androgen deprivation therapy; APA: apalutamide plus ADT; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gain; QALYs: quality-adjusted life years.								

The model results were most sensitive to the following scenario analysis parameters: selection of survival curves to extrapolate PFS; the method for the transition of patients between first and second line mHRPC health states; and the source of subsequent therapy market shares.

1.3 The decision problem: summary of the ERG's key issues

The ERG has not identified any key issues relating to the decision problem. However, please refer to Issue 2 (Clinical and cost effectiveness of apalutamide in people with mHSPC who are ineligible or unsuitable for docetaxel chemotherapy) where we discuss the implications of for the assessment of clinical effectiveness and cost effectiveness of the company's inclusion in the decision problem of a subgroup of people ineligible or unsuitable for docetaxel chemotherapy.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Issue 1 Selection of methods to adjust for treatment switching in the pivotal apalutamide clinical trials (nmHRPC and mHSPC)

Report section(s)	3.2.2 Risk of bias; 3.2.4 Trial statistical methods; 4.2.6, 4.2.7 and 4.2.8 Treatment effectiveness extrapolation methods.
Description of issue and why the ERG has identified it as important	There is uncertainty about the company's selection of the method to adjust survival outcomes to account for the effect of patients switching between treatments in the phase III pivotal clinical trials (SPARTAN and TITAN). Adjustment was required because of: • Patient crossover in the SPARTAN trial from placebo to apalutamide, and the potential bias from this on treatment effects in the intention to treat (ITT) analysis. • Current NHS England commissioning policy which restricts use of novel agents (apalutamide, abiraterone and enzalutamide) to once per patient. This meant adjusting the configuration of subsequent treatments used by patients in the multi-national SPARTAN and TITAN trials to reflect the subsequent treatments that would be available on the NHS (i.e. only one novel therapy during a patient's cancer treatment). A range of available adjustment methods for treatment switching were considered for their appropriateness to the available trial data and a justification given for the inclusion/exclusion of each. The company selected a (currently unpublished) 'modified' version of the Rank Preserving Structure Failure Time Model (RPSFTM) which uses external clinical trial data to adjust survival estimates. This approach avoids assumptions that conflict with the SPARTAN data. However, not all of its assumptions appear to be valid and the ERG is unable to independently verify the approach used.
What alternative approach has the ERG suggested?	The company declined the ERG's request to provide cost effectiveness scenario analyses based on the alternative adjustment methods for treatment switching, explaining that they give counter-intuitive / clinically implausible results, and because of insufficient trial data to satisfy assumptions. The ERG does not have access to the necessary patient level data to replicate these analyses.
What is the expected effect on the cost-effectiveness estimates?	Uncertain at present. Some of the assumptions of the modified RPSFTM approach may underestimate the cost effectiveness of apalutamide, whilst others potentially may over-estimate its cost effectiveness.
What additional evidence or analyses might help to resolve this key issue?	Treatment effect estimates can vary widely according to the adjustment methods chosen (and the assumptions therein). Cost effectiveness scenario analyses based on the alternative adjustment methods would indicate whether the ICERs are sensitive to different assumptions about

	treatment switching and allow a fully-informed committee consideration of the available evidence.

Issue 2 Clinical and cost effectiveness of apalutamide in people with mHSPC who are ineligible or unsuitable for docetaxel chemotherapy

Report section(s)	2.3 Critique of the decision problem; 3.2.5.6 Subgroup analysis; and 4.2.3 Economic model population.
Description of issue and why the ERG has identified it as important	The decision problem specifies a sub-group of mHSPC patients 'ineligible or unsuitable for chemotherapy'. An explicit definition of this subgroup is not given. A wide variety of patient factors can inform decisions about a given patient's suitability to tolerate the adverse effects of docetaxel. Cost-effectiveness estimates are presented separately for mHSPC patients who are: • Eligible/suitable for docetaxel (apalutamide plus ADT versus docetaxel plus ADT) and • Ineligible/unsuitable for docetaxel (apalutamide plus ADT versus ADT). There are no subgroup analyses in the pivotal TITAN trial based on docetaxel eligibility/suitability. Rather, clinical effectiveness estimates for docetaxel ineligible/unsuitable (apalutamide and ADT) are based on the whole trial population of the TITAN trial. A small proportion of patients in TITAN were/had been eligible to receive docetaxel, but it is unclear which characteristics could be used to reliably identify a group of patients considered ineligible/unsuitable to receive docetaxel. It is therefore uncertain whether the implicit assumption that the results of TITAN can be applied to patients ineligible to take docetaxel is valid.
What alternative approach has the ERG suggested?	Expert clinical opinion should be sought on the feasibility of identifying a sub-group of patients in TITAN with baseline characteristics indicative of docetaxel suitability/eligibility. If feasible, their survival outcomes could inform a post hoc subgroup analysis of clinical and cost effectiveness of apalutamide plus ADT versus ADT in patients considered ineligible/unsuitable for docetaxel treatment. Given the uncertainty regarding docetaxel eligibility/suitability criteria, and the statistical limitations of a post hoc subgroup analysis, this should be an exploratory scenario analysis.
What is the expected effect on the cost-effectiveness estimates?	Uncertain at present.
What additional evidence or analyses might help to resolve this key issue?	As stated above.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

Issue 3 Extrapolation of survival curves: metastatic free survival (MFS) for nmHRPC, and radiographic progression free survival (rPFS) for mHSPC

Report section(s)	4.2.7 Treatment effectiveness and extrapolation
Description of issue and why the ERG has identified it as important	The company's scenario analyses show that the choice of survival extrapolation for MFS/rPFS has a large impact on model results. There is some uncertainty about the most appropriate model survival curve, particularly for nmHRPC where there are no other clinical trials available with longer follow-up than the company's SPARTAN trial.
What alternative approach has the ERG suggested?	On the available evidence and advice from our clinical experts, we agree with the company's choice of the Weibull distribution for modelling MFS/rPFS.
What is the expected effect on the cost-effectiveness estimates?	In the company's analyses for nmHRPC, the ICER for apalutamide + ADT vs ADT varies from dominant (apalutamide cheaper and more effective) to £2,602 per QALY based on the log-normal distribution. For mHSPC, the ICER for apalutamide + ADT vs ADT varies from £25,329 per QALY to £40,355 per QALY, and vs docetaxel + ADT it varies from £38,983 per QALY to £68,613 per QALY (based on the exponential distribution).
What additional evidence or analyses might help to resolve this key issue?	Advice from clinical experts on the most clinically plausible extrapolation distributions for MFS/rPFS.

Issue 4 Utility values for second and third line metastatic hormone relapsed prostate cancer (mHRPC) health states

Report section(s)	4.2.10 Health related quality of life
Description of issue and why the ERG has identified it as important	Utility values were not assessed in the company's pivotal trials for patients who had progressed to the second and third-line of the mHRPC health state. The company based their values for second and third-line utility on those used in NICE TA387 (Abiraterone for mHRPC not previously treated with chemotherapy) and adjusted these values by applying a relative decline ratio to the utility for first-line mHRPC utility from TA387.
What alternative approach has the ERG suggested?	The ERG suggests that values from TA387 should be used without adjustment. We also suggest that scenario analyses should be conducted using utility values from other previous NICE appraisals, including NICE TA377 (Enzalutamide for mHRPC before chemotherapy is indicated) and NICE TA580 (Enzalutamide for nmHRPC) to estimate potential variability in cost-effectiveness based on a range of utility sources.
What is the expected effect on the cost-effectiveness estimates?	The ERG's changes to the utility values for mHRPC second line and third line have minimal effect on the comparison between apalutamide + ADT vs ADT, in both nmHRPC and mHSPC. For the comparison between apalutamide + ADT vs docetaxel + ADT, the ICER varies between £34,636 (using values from NICE TA387) and £43,475 per QALY (using values from NICE TA580).
What additional evidence or analyses might help to resolve this key issue?	We consider it is unlikely that there will be much, if any, additional published utility values for mHRPC which has not already informed previous NICE prostate cancer appraisals. Exploration of existing evidence (e.g. NICE TA580 and NICE TA377) could be informative in this current appraisal.

Issue 5 Market share of subsequent therapies used in metastatic hormone relapsed prostate cancer (mHRPC)

Report section(s)	4.2.114.2.11 Resources and costs
Description of issue and why the ERG has identified it as important	The company's scenario analyses show that the choice of market share for subsequent therapies for mHRPC have a large impact on the model results. The company sought estimates from their nmHRPC and mHSPC advisory boards, and then selected estimates from the mHSPC advisory board and applied them to both the nmHRPC and mHSPC indications. This assumes that patients in the mHRPC health state receive the same set of subsequent therapies after progressing from either nmHRPC or mHSPC. The company used estimates from the nmHRPC advisory board in scenario analyses.
What alternative approach has the ERG suggested?	Clinical advice to the ERG is that the company's estimated proportions of patients receiving the respective subsequent treatments are reasonable. However, the difference in ICERs according to which advisory board estimate is used requires further explanation. Further, the ERG notes that in the company's analysis a small proportion of patients with mHSPC treated with ADT alone received docetaxel as a subsequent treatment in the company. This is inappropriate for people ineligible/unsuitable for docetaxel in mHSPC, as by definition, they are not considered able to receive docetaxel. (However, due to the low cost of docetaxel), this is unlikely to have a large impact on the model results.
What is the expected effect on the cost-effectiveness estimates?	In the company's analysis for nmHRPC, apalutamide + ADT is dominant (cheaper and more effective) than ADT for both advisory board estimates of subsequent therapies market share. For mHSPC, the ICER for apalutamide + ADT vs ADT varies from £13,973 per QALY (scenario analysis - nmHRPC advisory board) to £25,329 (base case - mHSPC advisory board), and vs docetaxel + ADT the ICER varies from £9,633 per QALY (base case - mHSPC advisory board) to £31,311 per QALY (scenario analysis - nmHRPC advisory board).
What additional evidence or analyses might help to resolve this key issue?	Advice from clinical experts on the most clinically plausible estimates on the use of subsequent therapies for mHRPC, specific to patients progressing to mHRPC from nmHRPC and mHSPC, respectively.

Issue 6 Duration of adverse event costs for docetaxel (mHSPC)

Report section(s)	4.2.11 Resources and costs
Description of issue and why the ERG has identified it as important	The costs for treating adverse events associated with docetaxel have been applied for the whole pre-progression health state (2.7 years) in mHSPC.
What alternative approach has the ERG suggested?	We consider that the costs of adverse events for docetaxel treatment have been overestimated. Docetaxel is given for six cycles and the majority of the costs of treating side effects would be during this 18-week period. We therefore consider that adverse event costs should only be costed up to the trial follow-up duration (26 weeks).
What is the expected effect on the cost-effectiveness estimates?	The change suggested by the ERG increases the ICER for apalutamide + ADT vs docetaxel + ADT from £34,636 per QALY to £42,272 per QALY.
What additional evidence or analyses might help to resolve this key issue?	Feedback from clinical experts on managing docetaxel adverse events after 26 weeks.

The following issues identified by the ERG in the cost effectiveness evidence are not considered as key issues as they only have a small impact on model results:

- The approach to calculate mean health state durations for first, second and third line mHRPC health states;
- The duration of adverse event disutilities in the pre progression health state;
- Including unscheduled medical resource use costs.
- Cost of managing neutropenia
- Medical resource use

1.6 Other key issues: summary of the ERG's view

The ERG has not identified any other key issues.

1.7 Summary of ERG's preferred assumptions and resulting ICERs

Based on the ERG critique of the company's model (discussed in section 5.3.3), we have identified nine key aspects of the company base case with which we disagree. Our preferred model assumptions are the following:

1. **Extrapolation of OS for nmHRPC**: we use the generalised gamma model for OS because this is more consistent with the long-term survival estimates provided by our clinical experts (see section 4.2.7).
2. **Mean health state durations of first, second and third line mHRPC health states**: the ERG is unclear on the need to adjust the health state durations for the

proportion of patients not dying in the pre-progression state, as assumed by the company. Therefore, we use the unadjusted health state durations (see section 4.2.8.5).

3. **Mean health state duration of third line mHRPC**: We assume that the duration of third line mHRPC should be based on the time spent in both active treatment and best supportive care from NICE TA387, i.e. [redacted] for apalutamide plus ADT and [redacted] for ADT alone and docetaxel plus ADT (see section 0).
4. **Health state utilities for second and third line mHRPC health states**: We consider a more appropriate approach is not to adjust second and third line utilities by applying a relative decline ratio to the first line mHRPC utility value (that is, 0.625 for second line mHRPC and 0.5 for third line mHRPC (see section 4.2.10)).
5. **Duration of adverse event disutilities in the pre-progression health state**: We assume that the disutility from adverse events lasts for two weeks (see section 4.2.10).
6. **Duration of adverse events costs for docetaxel**: Docetaxel is given for six cycles and the majority of adverse events occur during this period. Therefore, we assume that applying the costs of docetaxel adverse events for a whole year is not adequate. The ERG applies a duration of six months as our preferred assumption (see section 4.2.11).
7. **Neutropenia cost**: We consider the company's cost an overestimation and assume that patients experiencing neutropenia would only require an additional outpatient visit and blood test, i.e. £150,16 (see section 4.2.11).
8. **Resource use**: To reflect clinical practice, we changed resource use according to the ERG's clinical advice (see section 4.2.11).
9. **Unscheduled medical resource use costs**: The company's rationale to include unscheduled medical resource use costs is unclear since AE disutility costs are already included. Therefore, we exclude these costs in our base case assumptions (see section 4.2.11).

The ICERs obtained using the ERG's preferred assumptions are shown in Table 4 and Table 5. Apalutamide plus ADT still dominates ADT alone in nmHRPC. In mHSPC, the ICER is £22,294 per QALY for the comparison between apalutamide plus ADT and ADT alone and £49,298 per QALY for the comparison between apalutamide plus ADT and docetaxel plus ADT.

Table 4 Cumulative cost-effectiveness results for ERG's preferred model assumptions for nmHRPC (discounted, PAS price for apalutamide)

Parameter	Treatment	Total costs	Total QALYs	ICER (£/QALY)
Corrected company base case	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ OS extrapolation: jointly fitted generalised gamma	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Unadjusted duration of mHRPC health states	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Mean health state duration for 3L based on the active treatment and BSC durations from TA387	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Unadjusted health state utilities for 2L/3L	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Duration of AE disutilities in the pre progression health state – 2 weeks	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Neutropenia cost – £150.16	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Resource use based on the ERG's clinical advice	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Exclude unscheduled MRU costs	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
ERG preferred model	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates

Table 5 Cumulative cost-effectiveness results for ERG's preferred model assumptions for mHSPC (discounted, PAS price for apalutamide)

Scenario	Treatment	Total costs	Total QALYs	ICER (£/QALY)	
				APA vs. DOX	APA vs. ADT alone
Corrected company base case	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£34,636	£25,002
+ Unadjusted duration of mHRPC health states	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£34,665	£25,009
+ Mean health state duration for 3L based on the active treatment and BSC durations from TA387	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£38,199	£25,944
+ Unadjusted health state utilities for 2L/3L	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£40,582	£25,096
+ Duration of AE disutilies in the pre progression health state – 2 weeks	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£41,581	£24,267
+ Duration of AE costs for docetaxel – 6 months	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£49,298	£24,267
+ Neutropenia cost – £150.16	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£50,227	£24,086
	ADT alone	[redacted]	[redacted]		

+ Resource use based on the ERG's clinical advice	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£50,377	£23,763
+ Exclude unscheduled MRU costs	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£49,298	£22,294
ERG preferred model	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£49,298	£22,294

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Janssen-Cilag Ltd on the clinical effectiveness and cost effectiveness of apalutamide (Erleada®) for the treatment of metastatic hormone-sensitive prostate cancer and non-metastatic hormone-relapsed prostate cancer. It identifies the strengths and weakness of the CS. Clinical experts were consulted to advise the evidence review group (ERG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the ERG via NICE on 11th August 2020. A response from the company via NICE was received by the ERG on 3rd September 2020 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

The NICE scope for this single technology appraisal (STA) encompasses both licensed therapeutic indications for apalutamide:

- In adult men for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT).
- In adult men for the treatment of non-metastatic hormone-relapsed prostate cancer (nmHRPC) who are at high risk of developing metastatic disease.

The ERG notes that:

- The NICE scope does not explicitly restrict the nmHRPC population to high-risk but the licenced indication for apalutamide does, hence the focus of the CS is on high-risk nmHRPC.
- Although the therapeutic indication for nmHRPC does not explicitly state that apalutamide should be given in combination with ADT, section 4.2 of the Summary of Product Characteristics (SmPC) states that treatment with gonadotropin releasing hormone analogue (i.e. ADT – the current standard of care) should be continued during apalutamide treatment.
- In line with previous appraisals for prostate cancer technologies, any recommendations made by NICE for apalutamide should apply to *adults* with prostate cancer, as both cisgender men and transgender women have a prostate. The term 'men' is only used when directly quoting the therapeutic indications as stated in the SmPC for apalutamide.

2.2.1 Background information on metastatic hormone-sensitive prostate cancer (mHSPC) and non-metastatic hormone-relapsed prostate cancer (nmHRPC)

Section B.1.3 of the company submission (CS) provides background information on the course of prostate cancer, focusing on the characteristics of the high-risk nmHRPC and the mHSPC patient groups, and their clinical management. The consequences of progression from these two patient groups to metastatic hormone relapsed prostate cancer (mHRPC) is also described. Below we summarise the key points relevant to this report.

2.2.1.1 High-risk nmHRPC

Among people with nmHRPC a proportion have 'high-risk' nmHRPC (committee slides for the NICE appraisal of enzalutamide for nmHRPC (TA580) state that an estimated 60% of nmHRPC patients are defined as high risk). The pivotal phase III apalutamide randomised controlled trial (RCT) included in the CS (the SPARTAN trial) defines high risk nmHRPC as having no detectable metastases on conventional imaging (CT and bones scans), hormone-relapsed prostate cancer (three prostate specific antigen (PSA) rises at least 1 week apart, with last PSA >2 ng/ml, despite castrate levels of testosterone <50 ng/dl), and a PSA doubling time (PSADT) of 10 months or less. This is a similar, but not identical, definition of high-risk nmHRPC used in the enzalutamide NICE appraisal (TA580) (high risk defined as an absolute PSA level ≥2 ng/mL and a PSADT of ≤10 months). The clinical experts consulted by the ERG indicated that although the concept of 'high-risk nmHRPC' is somewhat artificial, they did not disagree with it as a concept from a clinical perspective.

With the increasing use of positron emission tomography (PET) imaging in clinical practice, the number of patients classified as having nmHRPC is falling. This is because PET scanning, unlike conventional imaging, can identify very small metastases and, hence, more patients are diagnosed as having mHRPC.

2.2.1.2 mHSPC

mHSPC is a prostate cancer which is responsive to hormone therapy (i.e. patients have not yet developed hormone resistance) but it has spread from the prostate to more distant body sites such as bone, non-regional lymph nodes, the lung, the liver and the brain. The mHSPC patient group is heterogenous because some patients have 'newly diagnosed mHSPC' (i.e. mHSPC is the patient's initial prostate cancer diagnosis) but some patients have 'primary progressive mHSPC' (i.e. they have been previously diagnosed and are being or have been treated for localised disease and have then relapsed with mHSPC). Patients

who are newly diagnosed with mHSPC have not previously received hormone therapy, whereas those with primary progressive mHSPC are continuing to respond to hormone therapy (Figure 1) but the level and duration of response is limited. Expert clinical opinion to the ERG is that approximately half of mHSPC cases are newly diagnosed and half are primary progressive mHSPC With newly diagnosed patients having a poorer prognosis than patients with primary progressive mHSPC.[1 2] The mHSPC patient group is also heterogenous in terms of the site(s) of metastases, burden of disease, functional status and presence of cancer-related symptoms

2.2.2 Background information on apalutamide

CS Table 2 presents information on apalutamide (Erleada®), a second-generation non-steroidal anti-androgen that targets the androgen receptor (AR) with high affinity. By competitively inhibiting androgen binding to the AR, apalutamide prevents the sequence of events that would lead to the expression of androgen-regulated genes and inhibits prostate tumour progression.

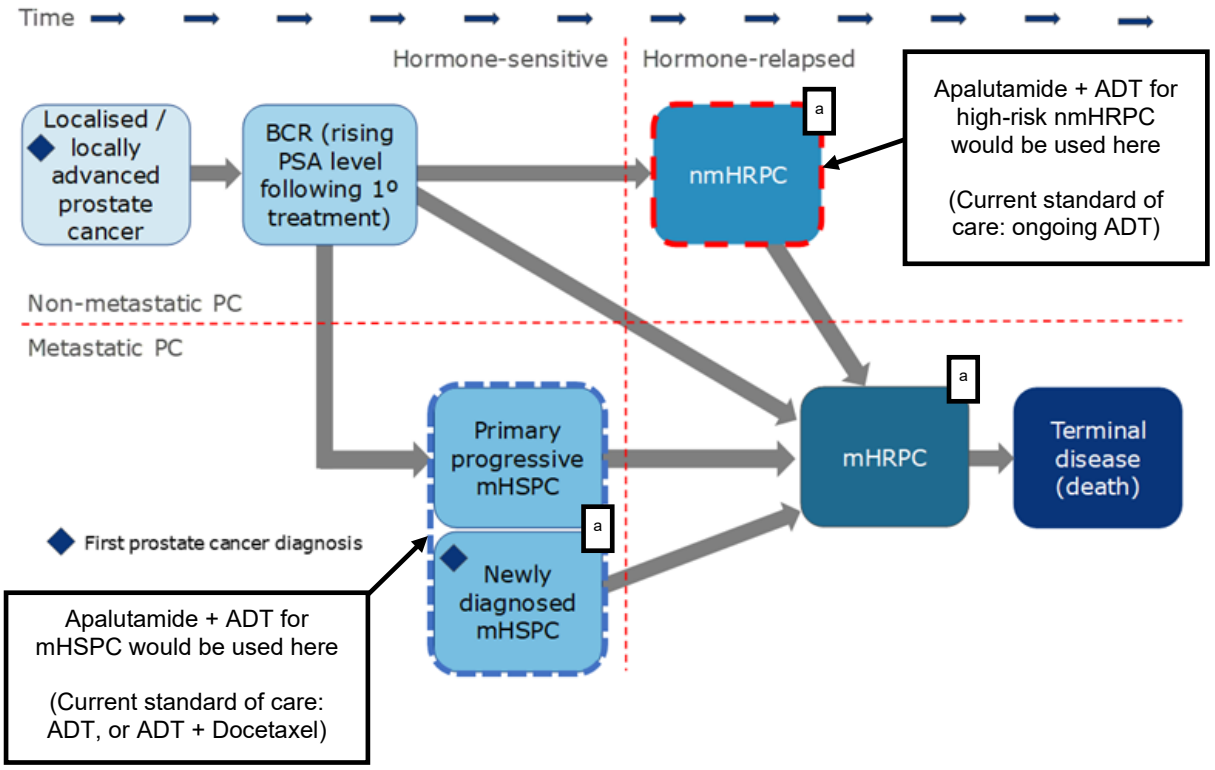
Marketing authorisation in Europe was received on 16th January 2019 for "the treatment adult men with high-risk nmHRPC" (for use in combination with ADT) and on 29th January 2020 for "the treatment of adult men with mHSPC in combination with ADT".

Apalutamide is administered orally as a single daily dose of 240mg (four 60 mg tablets) in combination with ADT. Treatment is intended to be continued until disease progression in both indications.

2.2.3 The position of apalutamide in the treatment pathway

In addition to the NICE prostate cancer guideline (NG131[3]) the European Association of Urology (EAU) and the European Society for Medical Oncology (ESMO) have also produced guidelines.[4 5]

The company outlines the clinical pathway of prostate cancer care in CS section B.1.3.3. Figure 1 shows the two places in the prostate cancer disease progression where apalutamide is licensed for use. In the non-metastatic prostate cancer setting (top half of Figure 1) apalutamide is intended to be prescribed in combination with ADT in adults with high-risk nmHRPC. In the metastatic prostate cancer setting (bottom half of Figure 1) apalutamide is intended to be prescribed in combination with ADT in adults with either primary progressive mHSPC or newly diagnosed mHSPC.



Abbreviations: BCR: biochemical recurrence; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; nmHRPC: non-metastatic hormone-relapsed prostate cancer; PC: prostate cancer; PSA: prostate-specific antigen.
Notes: Blue dashed borders depict the mHSPC patient group and the red dashed borders depict the nmHRPC patient group of interest to this submission.
[a] Clinical advice to the ERG is that death from other causes should be included in this figure, particularly for the nmHRPC group.

Source: Reproduced from CS Figure 2 with additional labelling indicating where apalutamide would be used added by the ERG

Figure 1 Prostate cancer disease progression and licensed use of apalutamide

For the high-risk nmHRPC patient group the current treatment pathway in the UK and the positioning of apalutamide is presented in CS Figure 6 and the pathway for the mHSPC patient group is presented in CS Figure 7. We summarise the information in these figures and the NICE pathway for managing metastatic prostate cancer[6] in Figure 2 below.

2.2.3.1 Treatment pathway for high-risk nmHRPC

As Figure 2 shows, the only treatment option currently available to patients in England with high-risk nmHRPC is to continue ADT until distant metastases develop (mean time to occurrence between 14.7 and 18.4 months in the placebo plus ADT arms of three clinical trials,[7] including the company's pivotal phase III SPARTAN trial,[8] for nmHRPC). Once patients have evidence of distant metastases, and thus have mHRPC, alternative anti-

cancer therapies become available. Apalutamide in combination with ADT would provide a new treatment option for patients with high-risk nmHRPC, with the goal of delaying the development of mHRPC.

NICE guidance does not recommend the use of enzalutamide for nmHRPC (TA580[9]) hence why it was not considered a comparator treatment in the current appraisal. A NICE appraisal of darolutamide with ADT for treating nmHRPC (NICE ID1443[10]) is in development (first NICE Appraisal Committee meeting 9th September 2020, expected publication 25 November 2020). Darolutamide was not included as a comparator in the scope of this appraisal as at the current time a NICE recommendation has not been published.

Disease stage	High-risk nmHRPC
Current treatment option	Continue ADT
Positioning of apalutamide	Apalutamide + ADT

Disease stage	mHSPC
Current treatment options	ADT
	Docetaxel + ADT
Positioning of apalutamide	Apalutamide + ADT

Disease stage	mHRPC		
	First-line	Second-line	Third-line
Current Treatment options	Docetaxel[a]	Docetaxel	Cabazitaxel [b]
	Abiraterone [c]	Abiraterone [c]	Abiraterone [c]
	Enzalutamide [c]	Enzalutamide [c]	Enzalutamide [c]
	[d]	Radium-223 [e]	Radium-223 [f]
	Corticosteroids [g]	Corticosteroids [g]	Corticosteroids [g]

[a] For eligible patients who did not receive docetaxel in the mHSPC setting
[b] In people whose disease has progressed during or after docetaxel chemotherapy
[c] Patients can receive either abiraterone or enzalutamide but not both.
[d] Empty cells indicate the treatment that is shown in that row for other disease stages is not a treatment option
[e] Radium-223 dichloride is an option for mHRPC in people with symptomatic bone metastases and no known visceral metastases if docetaxel is contraindicated or not suitable for them
[f] Radium-223 dichloride is an option for mHRPC in people with symptomatic bone metastases and no known visceral metastases if they have already had docetaxel
[g] Corticosteroids can be considered at any stage if other treatment options are contra indicated

Figure 2 Current treatment pathway for high-risk nmHRPC, mHSPC and mHRPC in England including the positioning of apalutamide

2.2.3.2 Treatment pathway for mHSPC

For patients with mHSPC in England there are two potential treatment options: ADT or, for patients who are considered fit enough, docetaxel may be used off-label [NB. Docetaxel is licenced for the treatment of metastatic hormone-resistant prostate cancer (mHRPC). Docetaxel is not licensed for mHSPC, but NHS England commissions it for up to 6 cycles]. The ERG notes that whilst docetaxel is not suitable for all patients (due to clinical features such as performance status and comorbidities), some patients who are eligible to receive docetaxel will choose not to receive it at this point in their treatment (they may potentially choose to receive docetaxel later in the disease course).

The National Prostate Cancer Audit (NPCA), Annual Report 2019[11] states that 27% of adults with newly diagnosed metastatic disease received docetaxel in combination with standard ADT (range 0% to 39% by NHS provider in England). The NPCA report states that they expect the proportion of patients with newly diagnosed metastatic disease who receive docetaxel to increase in future years[11] but we note that this expectation was published before the COVID-19 pandemic. During the advent of the COVID-19 pandemic in early 2020 NHS England allowed the option to give enzalutamide with ADT for patients with newly diagnosed metastatic disease (administered orally at home), instead of docetaxel by intravenous infusion in hospital. The rationale is to reduce the requirement for hospital attendance, and also to reduce toxicity-related hospital admissions, both of which increase the potential for hospital-acquired coronavirus infection.[12] Patients intolerant of enzalutamide have the option to switch to abiraterone, which is also administered orally at home. Therefore, use of docetaxel will have decreased during the COVID-19 pandemic in 2020, and lower use may continue into 2021 depending on the (currently uncertain) course of the pandemic.

The CS states that ADT is not a life-prolonging treatment for patients with mHSPC, however the ERG believes it is more appropriate to state that it is not clear whether ADT improves survival in patients with mHSPC. One of the ERG's clinical advisors accepted that there is no level 1 evidence (i.e. systematic reviews of RCTs) available for to confirm the benefit of ADT on OS, but stated that it is the gold standard treatment for metastatic prostate cancer and it is considered to be life-prolonging. Apalutamide in combination with ADT would provide a new treatment option for patients with mHSPC, particularly for those who are not eligible for or who are unwilling to receive treatment with docetaxel, and in particular during the COVID-19 pandemic when docetaxel treatment is not recommended in interim guidance.[12] The goal of treatment is to delay disease progression and thus delay the development of mHRPC.

ERG conclusion

The CS provides a detailed description of the course of prostate cancer disease, and the characteristics of the high-risk nmHRPC and mHSPC patient groups and the subsequent progression to mHRPC. It adequately describes the limited treatment options that are currently available for these two patient groups and demonstrates the potential role of apalutamide in combination with ADT as an alternative treatment option.

2.3 Critique of the company's definition of the decision problem

Table 6 summarises the decision problem addressed by the company in the CS, in relation to the final scope issued by NICE and the ERG's comments on this. Aside from the issues described below, the company's decision problem either matches the NICE scope or the differences are minor and the ERG does not have any concerns about them.

The issues of uncertainty or disagreement between the NICE scope and the company's decision problem that we have identified are:

- The company have limited the nmHRPC population to people with high-risk nmHRPC. This is consistent with the marketing authorisation for apalutamide ("the treatment adult men with high-risk nmHRPC"). However, the ERG notes that there is no consistent definition in clinical practice for high-risk nmHRPC
- The CS decision problem does not include the two subgroups listed in the NICE scope, that is, people with **newly diagnosed** metastatic prostate cancer and people with **high-risk** metastatic prostate cancer).
    - For the nmHRPC population CS Figure 2 indicates people are not newly diagnosed with nmHRPC (they will have progressed to nmHRPC after primary treatment for localised/locally advanced prostate cancer) and they do not yet have metastases so neither of the subgroups appear relevant for the nmHRPC population.
    - For the mHSPC population a distinction can be made between newly diagnosed and primary progressed patients (and, as already described, the mHSPC patient group is a heterogenous population in other respects too). It is known that newly diagnosed patients have a poorer prognosis than patients with primary progressive mHSPC.[1 2] Therefore, whilst there is justification for a subgroup analysis of newly diagnosed mHSPC patients the company haven't commented on the feasibility of this. Identifying patients with high-risk mHSPC is typically based on prognostic factors such as metastatic burden,

metastasis location, time of metastatic presentation and Gleason score but there does not appear to be an agreed definition of high-risk mHSPC and key clinical trials (CHAARTED[14] and LATITUDE[15]) have used different criteria to identify high-risk patients. It is less clear whether there would have been justification for a subgroup analysis based on high-risk mHSPC but again the company have not commented on this.

- The decision problem specifies a sub-group of mHSPC 'patients ineligible or unsuitable for chemotherapy', stating that unmet need is highest in this group. The ERG considers this an appropriate justification but notes that the features that define this subgroup of patients are not defined in the decision problem or elsewhere in the CS. Base case cost-effectiveness results are presented for mHSPC patients who are eligible for docetaxel (apalutamide plus ADT versus docetaxel plus ADT) and for those who are ineligible for docetaxel (apalutamide plus ADT versus ADT). However, clinical effectiveness data are not presented separately for these subgroups and it is not explicitly stated in the decision problem or the formative sub-sections of the clinical effectiveness section (B.2) that the TITAN trial results are intended to be applicable to docetaxel ineligible patients. We discuss this issue later in this report (section 4.2.3).
- We agree that it is appropriate to have excluded abiraterone plus ADT and enzalutamide plus ADT, as comparators because the NICE appraisals for these are still currently ongoing.

Table 6 Summary of the decision problem

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG comments
Population				
nmHRPC	Adults with nmHRPC	Adults with high-risk nmHRPC	The marketing authorisation for apalutamide in nmHRPC is for those at high risk of developing metastatic disease,[a] as per the SPARTAN trial.	There is no consistent definition in place for 'high-risk nmHRPC'. In the CS the definition from the phase III SPARTAN trial is used.[b]
mHSPC	Adults with mHSPC	Adults with mHSPC	N/A	Decision problem matches the NICE scope
Intervention				
nmHRPC and mHSPC	Apalutamide plus ADT	Apalutamide plus ADT	N/A	Decision problem matches the NICE scope
Comparator(s)				
nmHRPC	ADT	ADT	N/A	Decision problem matches the NICE scope
mHSPC	• ADT • Docetaxel with ADT • Abiraterone with prednisone or prednisolone and ADT (subject to ongoing NICE appraisal) • Enzalutamide with ADT (subject to ongoing NICE appraisal)	• ADT • Docetaxel with ADT	• Abiraterone received a 'not recommended' in the NICE FAD released in June 2020. As such, it cannot be considered a relevant comparator • Enzalutamide with ADT is currently being appraised by	The company have omitted two comparators from the scope: abiraterone + ADT and enzalutamide + ADT. The ERG notes that these appraisals are currently

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG comments
			NICE. As such, it cannot be considered a relevant comparator	ongoing so it is appropriate to exclude them.
Outcomes				
nmHRPC	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rate • PSA response • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Overall survival • Metastases-free survival • Progression-free survival • PSA response • Adverse effects of treatment • Health-related quality of life measures • Time to symptomatic progression • Time to PSA progression • Second progression-free survival • Time to initiation of cytotoxic chemotherapy • Time to metastasis	As per scope, and additional outcome measures provide supportive efficacy data for apalutamide.	The company have not included response rate as an outcome measure which is acceptable because this was not an outcome. Captured in the company's RCT for this population.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG comments
mHSPC	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rate • PSA response • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Overall survival • Radiographic progression free survival • Progression-free survival • PSA response • Adverse effects of treatment • Health-related quality of life • Second progression free survival	As per scope and additional outcome measures provide supportive efficacy data for apalutamide.	Although the company do not list response rate as an outcome measure the outcome 'Best overall response' is reported for this population.
Subgroups of interest				
mHSPC	• people with newly diagnosed metastatic prostate cancer • people with high-risk metastatic prostate cancer	patients ineligible or unsuitable for chemotherapy	Unmet need is highest in these patients	The CS does not include the subgroups listed in the NICE scope. The CS presents separate base-case cost-effectiveness results for mHSPC patients who are docetaxel eligible/ineligible. However, effectiveness data are not

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG comments
				presented separately for these subgroups.

Source: CS Table 1 with minor formatting alterations and column added for ERG comments
ADT: androgen deprivation therapy; ERG: evidence review group; MA: marketing authorization; mHSPC: metastatic hormone-sensitive prostate cancer; N/A, not applicable; NHS: National Health Service; nmHRPC: non-metastatic hormone-relapsed prostate cancer; PSA: prostate-specific antigen; PSADT: PSA doubling time
[a] A high risk for the development of metastases is defined as PSADT ≤10 months during continuous ADT
[b] The SPARTAN trial definition of high-risk nmHRPC is: detectable metastases on conventional imaging, hormone-relapsed prostate cancer (three PSA rises at least 1 week apart, with last PSA >2 ng/ml, despite castrate levels of testosterone <50 ng/dl), and a PSADT of 10 months or less].

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company carried out two systematic literature reviews (SLRs), one for the nmHRPC patient group and one for mHSPC patient group. Their literature search and review methods are reported in CS B.2.1-B.2.2 and in CS Appendix D. Below we critically appraise these reviews.

3.1.1 Clinical effectiveness review of nmHRPC treatments

The SLR for nmHRPC included the whole nmHRPC patient population, not only the high-risk nmHRPC population in the company's decision problem. The literature search included core medical databases (Medline, Medline in Process, Embase, Cochrane Database of Systematic Reviews (CDSR), Cochrane CENTRAL), all NICE recommended websites, and several relevant conferences of the past three years. Databases were searched from database inception and the several update searches reported provided coverage up until the beginning of June 2020. The trial registry ClinicalTrials.gov was searched in the penultimate search update with a limit to include only trials with published results.

Table 7 gives an overview of the company's approach to the SLR of nmHRPC studies, with references to further discussion where relevant. Overall the ERG believes the SLR to be of good quality and unlikely to be biased.

Table 7 ERG appraisal of systematic review methods for nmHRPC

Systematic review components and processes	ERG response (Yes, No, Unclear)	Comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	The framework for the eligibility criteria uses a variation of PICO as reported in CS Table D.23. The structure of the searches reflects this.
Searches: was the literature review carried out appropriately (sources, date range, in line with PICOD, correct search terms/syntax, etc.)?	Yes	Reported in CS Appendix D.1. The original search was weak regarding search terms and overall strategy. A greatly improved search was employed from the first update onwards which also searched the previous date period to compensate.
Searches: were any relevant studies missed?	No	Appears to be a gap in Embase date coverage between 29/11/2018 and 01/07/2019 – a targeted search in Embase by the ERG did not find anything missing.

Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes	Reported in CS Table D.23. A broader nmHRPC population than the company's decision problem – the latter is restricted to *high-risk* nmHRPC patients. No specific interventions or comparators were specified. The review included RCTs measuring survival, disease progression, QoL scores and safety outcomes.
Were study selection criteria applied by two or more reviewers independently?	Yes	Database records and full texts of potentially relevant studies were assessed by two independent reviewers with a third, senior, reviewer to resolve any discrepancies. Records from other sources were assessed by a single independent reviewer.
Was data extraction performed by two or more reviewers independently?	Yes	Two independent reviewers with a third, senior, reviewer to resolve any discrepancies.
Was a risk of bias assessment or a quality assessment of the included studies undertaken? **If so, which tool was used?**	Yes	Reported in CS B.2.5 and CS Table 11. Further details are in Appendix D.5.1 (Table D.55). The company adapted the NICE single technology appraisal user guide for company evidence submission and the Centre for Reviews and Dissemination guidance for undertaking reviews in health. Discussed further in section 3.2.2 of this ERG report.
Was risk of bias assessment (or other study assessment) conducted by two or more reviewers independently?	Unknown	Not reported.
Is sufficient detail on the individual studies presented?	Yes	CS Tables D.24 and D.25 report references and key attributes of included studies. One relevant study appears to be missing as the PRISMA flow diagram reports 12 relevant RCTs whereas Table D.25 reports details of 11 studies. CS Table. D.26 reports excluded studies with reason for exclusion. Full details of the SPARTAN trial are presented in CS B.2 and section 3.2.1 of this report.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Not applicable	A meta-analysis was not possible as only one trial of apalutamide in nmHRPC was identified (SPARTAN). The company justifies not doing an ITC because a direct comparison with ADT was

		possible from SPARTAN. See section 3.3 of this report.

3.1.2 Clinical effectiveness review of mHSPC treatments

The SLR of the clinical effectiveness in mHSPC searched the literature for randomised and non-randomised controlled trials. All relevant sources, including grey literature, were searched as for the nmHRPC SLR above. Databases were searched from database inception and the several update searches reported provided coverage up until the beginning of June 2020.

Table 8 below gives an overview of the company's approach to the SLR of mHSPC treatment clinical effectiveness studies, with references to further discussion where relevant. Overall, the ERG considers the company's SLR to be of good quality and unlikely to be biased.

Table 8 ERG appraisal of systematic review methods for mHSPC

Systematic review components and processes	ERG response (Yes, No, Unclear)	Comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	PICOS template was predefined and used for screening. Reported in Tables D.45 and D.46. The non-RCT PICOS is more specific than the RCT PICOS: the intervention concept is searching for apalutamide studies or combination therapy studies only. The non-RCT search was conducted in case anything relevant would be missed from the RCT search. mHSPC is a narrow population and other elements of the PICO search, e.g. study type, can be made broader in order not to miss relevant studies.
Searches: was the literature review carried out appropriately (sources, date range, in line with PICOD, correct search terms/syntax, etc.)?	Yes	Reported in CS Appendix D.2. Overall, the literature searches were comprehensive. Tables of the original and first update search strategies for mHSPC are combined meaning reported search yield is unclear whether for either or both searches.
Searches: were any relevant studies missed?	No	The ERG believes that no relevant studies would have been missed. The non-RCT search did not identify any relevant prospective interventional studies.

Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem	Unclear	Reported in Tables D.45 (for RCTs) and D.46 (for non-RCTs) – the only difference being study design and that the non-RCT search only included apalutamide or combination therapy studies.
Were study selection criteria applied by two or more reviewers independently?	Yes	Review was carried out by two independent researchers.
Was data extraction performed by two or more reviewers independently?	Yes	Review was carried out by two independent researchers. For this stage, where there was a lack of consensus, a third independent researcher resolved any discrepancies.
Was a risk of bias assessment or a quality assessment of the included studies undertaken? **If so, which tool was used?**	Yes	Summary assessment in CS B.2.5 and CS Table 11. Further details in Appendix D.5.2 (Table D.56). The company adapted the NICE single technology appraisal user guide for company evidence submission and the Centre for Reviews and Dissemination guidance for undertaking reviews in health. Discussed in section 3.2.2 of this report.
Was risk of bias assessment (or other study assessment) conducted by two or more reviewers independently?	Unknown	Conduct of assessment not reported.
Is sufficient detail on the individual studies presented?	Yes	CS Tables D.47 and D.48 report references and key attributes of included records. CS Table. D49. Reports excluded studies with reason for exclusion. The included studies are discussed further in section 3.2.1 of this report.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Yes	A network meta-analysis was undertaken for apalutamide plus ADT versus docetaxel plus ADT. Reported in CS B.2.15.1 and discussed in section 3.3 of this report.

ERG conclusion

The CS reports two comprehensive clinical effectiveness literature searches, one each for the two patient groups in this appraisal. The ERG considers the reported methods for inclusion/exclusion reference screening to be appropriate. The CS appendices present all the search strategies, use the PRISMA flow diagram for cumulative results of all the original and update searches, and provides lists of excluded studies with reasons for exclusion. The ERG does not believe that any relevant clinical effectiveness studies have been missed by the company's literature searches.

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

The company's SLR identified two clinical trials of apalutamide relevant to the decision problem:

- the SPARTAN trial of apalutamide for the treatment of high risk nmHRPC[8 16-19]
- the TITAN trial of apalutamide for the treatment of mHSPC[20 21]

Both trials are company-sponsored, phase III randomised, double-blind, placebo-controlled, multinational, multi-centre trials. The ERG is satisfied that the company search has identified all studies for apalutamide that are relevant to the decision problem.

3.2.1.1 Study characteristics

The trial methodologies used in SPARTAN and TITAN are described in CS sections B.2.3.1 and B.2.3.2, respectively, and summarised in CS Table 6. We show an overview of the trial characteristics in in Table 9 below. A list of pre-planned sub-group analyses are provided in CS Table 6 and are described in more detail in section 3.2.4 of this ERG report.

Table 9 Summary of trial characteristics

Trial characteristic	SPARTAN	TITAN
Study design	Phase III randomised double-blind, placebo controlled, parallel group	Phase III randomised, double-blind, placebo controlled, parallel group
Number and location of centres	332 sites across 26 countries in North America, Europe & Asia-Pacific regions. 15 UK sites (n=99 UK patients).	260 sites across 23 countries in North and South America, Europe & Asia-Pacific regions. 10 UK sites (n=36 UK patients).
Study population	Men ≥18 years with high risk nmHRPC	Men ≥18 years with mHSPC and at least one bone lesion
Intervention (no. randomised)	Apalutamide 240mg once daily plus ADT (n=806) Continuous treatment in 28-day treatment cycles	Apalutamide 240mg once daily plus ADT (n=525) Continuous treatment in 28-day treatment cycles
Comparator (no. randomised)	Placebo plus ADT (n=401)	Placebo plus ADT (n=527)
Primary outcome(s)	Metastases free survival (MFS)	Radiographic progression free survival (rPFS) and overall survival (OS)
Randomisation ratio	2:1	1:1

Trial characteristic	SPARTAN	TITAN
Stratification factors	PSA doubling time (>6 months vs ≤6 months), use of bone-sparing agents and classification of nodal disease (local, N0 vs regional N1)	Gleason score, prior docetaxel use and region
Status	Complete, published.	Ongoing. Final results for rPFS outcome published. Final OS results unpublished.
Latest available data	1st February 2020 (final data cut)	23rd November 2018
Median duration of follow up (months)	19th May 2017 IA1 data cut: 20.3 1st Feb 2019 IA2 data cut: 41.0 1st Feb 2020 final data cut: 52.0	23rd Nov 2018 IA1 data cut: 22.7
No. (%) of discontinuations	19th May 2017 Apalutamide plus ADT: [redacted] (39%) Placebo plus ADT: [redacted] (70%) 1st Feb 2020 Apalutamide plus ADT: [redacted] Placebo plus ADT: [redacted]	23rd Nov 2018 Apalutamide plus ADT: [redacted] Placebo plus ADT: [redacted]
No. (%) of crossovers from placebo to open-label active arm at unblinding[a]	76 (19%) of whom 46 continued to receive apalutamide as of the clinical cut-off date for the final analysis (Feb 2020) in this submission.	Number not reported in CS as data was not available at the time of the first interim analysis.
No. (%) using one or more subsequent life-prolonging prostate cancer therapies	Apalutamide plus ADT:371 (46.0%) Placebo plus ADT:279 (69.6%) Denominator: ITT population	Apalutamide plus ADT:64 (37.6%) Placebo plus ADT:165 (60.9%) Denominator: number of patients alive at treatment discontinuation

ADT: androgen deprivation therapy; IA: interim analysis; MFS: metastatic-free survival; OS: overall survival; rPFS: radiographic progression-free survival;
Source: CS Tables 4-6, CS section B.2.3, CS Appendix D.4, SPARTAN CSR Tables 4 & TSIDEM02[22] Response to Clarification Question A5 Table 2.
[a] Both trials were unblinded after results of the first interim analyses showed evidence of effectiveness for apalutamide versus placebo for the trials' primary outcomes and patients randomised to placebo were subsequently allowed to crossover to the apalutamide arm.

3.2.1.2 The SPARTAN trial

The SPARTAN trial[8 16-19] compared the efficacy and safety of apalutamide 240mg orally daily plus ADT with placebo plus ADT in adult men with nmHRPC. The patient population comprised people with histologically or cytologically confirmed prostate cancer that was defined as:

- Non-metastatic: no detectable metastases on conventional imaging (CT and bone scans) assessed by blind independent central review (BICR),

- Hormone-relapsed: three prostate-specific antigen (PSA) rises at least 1 week apart, with last PSA>2ng/ml, despite castration levels of testosterone <50ng/ml), and
- High-risk: PSA doubling time of less than or equal to 10 months. Clinical experts to the ERG noted that the concept of 'high-risk' nmHRPC is largely used to provide a standardised definition in the trial setting, rather than for use in clinical practice for patient management. They did not disagree with the concept and they acknowledge that it defines the population most likely to benefit from treatment. Our clinical experts did not mention any alterative risk stratification criteria used in practice.

ADT consisted of continuous treatment with a gonadotrophin-releasing hormone (GnRH) analogue (where surgical castration had not occurred). The choice of ADT (agonist or antagonist) was at the discretion of the investigator and dosed according to the product's label. Most patients used a GnRH analogue ([redacted] in the apalutamide arm and [redacted]% in the placebo arm; based on safety population, SPARTAN CSR Table TSICM01).[22] Study treatment continued until disease progression, withdrawal of consent, or unacceptable treatment-related toxicity.

Data cuts for SPARTAN are described in CS Table 4. The first interim data cut (19th May 2017) was used as the final analysis for the primary endpoint of metastatic-free survival (MFS) while the final data cut (1st Feb 2020) was used for the analysis of longer term outcomes such as overall survival (OS) and second progression-free survival (PFS2). Trial outcomes for SPARTAN are described in more detail in section 3.2.3 of this ERG report. SPARTAN informs the economic model by providing comparative evidence of clinical effectiveness of apalutamide plus ADT versus placebo plus ADT for the outcome of MFS and longer-term outcomes of PFS2 and OS.

3.2.1.2.1 Patient crossover from placebo plus ADT to apalutamide plus ADT

Following advice from the trial's Independent Data Monitoring Committee (IDMC), the trial was unblinded at the first interim analysis due to evidence of superiority of apalutamide over placebo for the primary endpoint, MFS. Patients in the placebo arm were thus offered the option of crossing over to open-label apalutamide therapy at this point. Of the 76 (19%) patients randomised to placebo who crossed over, 46 continued and 30 discontinued open label apalutamide as of February 2020. In addition, patients who reached the primary endpoint of MFS were permitted to receive one or more subsequent therapies to treat

metastatic hormone-relapsed prostate cancer (mHRPC). These included novel therapies such as abiraterone plus prednisolone (provided as per protocol by the sponsor) or enzalutamide, chemotherapy or radium-223 therapy (CS Table 16). One or more of these subsequent treatments were used by a higher percentage of patients in the placebo plus ADT arm (69.6% of 401 patients) compared to the apalutamide plus ADT arm (46.0% of 806 patients). This refers to use of subsequent therapy considered to be life-prolonging in prostate cancer regardless of when used; i.e. an individual patient may have used more than one different type of subsequent therapy.

The crossover from placebo plus ADT to apalutamide plus ADT may potentially bias ITT results at the final analysis in favour of placebo plus ADT. The imbalance between the trial arms in the proportions of patients who use of subsequent treatments is not necessarily a source of bias, as it may reflect a difference in rates of progression to metastatic disease. However, enzalutamide and abiraterone would not be available as subsequent therapy to patients treated with apalutamide as current NHS England policy restricts use of these novel agents to once per patient. Thus, while switching from placebo to just one of the novel agents would reflect current clinical practice for patients receiving ADT alone, subsequent use of a second novel agent would not be permitted. In contrast, switching from apalutamide to any other novel agent would not be permitted in practice. In SPARTAN, use of subsequent therapy not permitted in the NHS was reported in [redacted] patients in the apalutamide plus ADT arm (who subsequently used abiraterone or enzalutamide), while [redacted] of patients in the placebo plus ADT arm subsequently used both abiraterone and enzalutamide. The higher use of NHS non-permitted (subsequent) novel therapy in the apalutamide plus ADT arm of the trial may potentially over-estimate its effect (though this effect may be reduced due to cross-resistance between the novel therapies). However, it potentially counters the bias favouring placebo plus ADT arising from crossover. The company's choice of statistical methods to address potential bias from treatment switching are further discussed later in this ERG report (section 3.2.2 (Risk of bias), section 3.2.4 (Trial statistical methods), and sections 4.2.6, 4.2.7 and 4.2.8 (Treatment effectiveness extrapolation methods).

3.2.1.3 The TITAN trial

The TITAN trial[20 21] compared the efficacy and safety of apalutamide 240mg orally daily plus ADT with placebo plus ADT in adult men with mHSPC. The patient population comprised men with prostate cancer that was metastatic defined by one or more documented bone lesions. Clinical experts to the ERG advised that approximately 60%-85% of mHSPC

patients present with bone metastases. Patients with only visceral metastases or only lymph node involvement were not included in the trial. One ERG clinical expert noted that such patients were not excluded from other pivotal RCTs in this disease population. The company suggest that around 10% of mHSPC patients have only visceral metastases, however, expert advice to the ERG suggests that this proportion is likely to be smaller and that more patients would have only lymph node disease. Expert advice confirmed that the extent/site of metastases may affect prognosis. Patients with only lymph node involvement would typically have better outcomes than those with bone metastasis. Those with visceral metastases would have the poorest outcomes but most of these patients will also have bone metastases. While the trial population may under-represent patients without bone disease, it remains unclear as to whether the treatment effect for apalutamide is likely to differ between mHSPC patients with and those without bone disease.

ADT (medical or surgical castration) must have been started at least 14 days before randomisation and continued during the trial. Prior ADT therapy was restricted to a maximum of six months duration prior to randomisation in the metastatic disease stage and no more than three years in total for prior ADT therapy started during the non-metastatic disease stage. Use of ADT during the trial comprised mainly GnRH agonists ([redacted]% for the apalutamide arm and [redacted]% in the placebo arm. (CSR Table TSICM01)[23] Prior docetaxel chemotherapy for metastatic disease was permitted if disease did not progress on or after this treatment.

The CS presents results from the first interim analysis (at 23rd Nov 2018) which provides final data for the co-primary endpoint of radiographic progression-free survival (rPFS) and interim (immature) data for the co-primary endpoint of overall survival. The study is ongoing (estimated completion date 12th July 2021).[24] Trial outcomes for TITAN are described in more detail in section 3.2.3 of this ERG report. TITAN informs the economic model by providing comparative evidence of clinical effectiveness for the outcome of rRFS, PFS2 and OS for apalutamide plus ADT versus placebo plus ADT. In addition, a network meta-analysis provides indirect evidence of comparative effectiveness between apalutamide plus ADT and docetaxel chemotherapy plus ADT.

The TITAN trial's IDMC also recommended unblinding of the study at the first interim analysis due to evidence of a survival benefit with apalutamide for the co-primary endpoint, rPFS. Patients randomised to placebo plus ADT were offered an option to crossover to open-label apalutamide plus ADT. The first interim analysis data cut presented in the CS is unaffected by this crossover. However, analysis of longer-term outcomes (OS and PFS2)

may be biased (in favour of placebo) by the crossover to apalutamide. Use of one or more subsequent life-prolonging therapies which was higher in the placebo (plus ADT) arm (60.9% of the 271 patients who were alive at treatment discontinuation) compared to the apalutamide arm (37.6% of 170 patients) (Response to Clarification Question A5; Table 2). This difference in proportions does not necessarily represent a source of bias, as it might just reflect a greater rate of progression in the placebo plus ADT arm. However, the use of more than one novel subsequent therapy ([redacted] patients in the apalutamide arm versus [redacted] patients in the placebo arm) may introduce a bias in favour of apalutamide as this would not be permitted under current NHS policy, as described earlier. These potential biases and methods to address them are further discussed in section 3.2.2 and 3.2.4 of this ERG report.

3.2.1.4 Patients' baseline characteristics

The baseline characteristics of patients in SPARTAN and TITAN are summarised in Table 10. All characteristics were well balanced between trial arms in both studies.

Expert clinical advice to the ERG suggests that the reported patient characteristics in both trials are representative of patients seen at the respective disease stages in clinical practice. An exception is that in the TITAN trial, the majority of patients with mHSPC were newly diagnosed (81% with M1 stage at diagnosis, see Table 10 below), whereas expert clinical advice to the ERG suggests that in practice around 50% of patients are newly diagnosed at the metastatic stage, while the other 50% have progressed to metastases from localised or locally advanced prostate cancer (primary progressive mHSPC).

Table 10 Baseline characteristics

Patient Characteristic	ERG comment	
	SPARTAN	TITAN
Age	The mean (SD) age of patients was 73.9 (8.02) years. This is as expected given most men with prostate cancer are diagnosed between 65 and 69 years [25] and men in this study had a median duration of [redacted] years since diagnosis	The mean age of patients was younger (68.4 years; SD 8.28) compared to the SPARTAN trial. Men with mHSPC in TITAN were more recently diagnosed (median time since initial diagnosis was 4 months) than men presenting with nmHRPC in SPARTAN.
Race	The majority of patients were White (66.3%). This is lower than the	68.3% of men were White. As in SPARTAN, this is lower than in the

Patient Characteristic	ERG comment	
	SPARTAN	TITAN
	general UK population, particularly in men aged over 60. The ERG did not find any published ethnicity distributions for the English disease population but note that the risk of prostate cancer is higher in Black men compared to White men.[26]	general UK population but may reflect the higher risk of prostate cancer in Black men.
Risk stratification/ disease severity indicators	• Most men (75.3%) had tumour grade ≥T2, • 43.6% of men had Gleason scores >7, • [redacted]% of men had no spread to regional lymph nodes (stage N0) at diagnosis, • Baseline median PSA was 7.80 ng/ml., • Mean (SD) PSA doubling time was [redacted]) months	• Most men had stage M1 metastases (81.0%), • 67.3% of men had Gleason scores >8, • 53% had bone metastases only, • 61.7% had ≤10 bone lesions, • 62.7% had high volume disease,
ECOG performance status score	Most patients (77.4%) had an ECOG score of 0 reflecting no impairment on functional status	Most patients (64.3%) had an ECOG score of 0 reflecting no impairment on functional status
Prior and concomitant ADT treatment	The majority [redacted]%) of men used GnRH agonists prior to and during the study. This is consistent with UK practice. Clinical experts to the ERG reported that goserelin and leuprorelin are the most commonly used medical castration treatments.	Over 90% of men used GnRH agonists prior to the study and approximately [redacted]% used these agents during the study. This is in keeping with UK clinical practice.
Prior surgery or radiotherapy for localised prostate cancer	Most men ([redacted]%) had had a prostatectomy or radiation therapy. This reflects current NICE guidance whereby patients with high-risk localised disease would be offered radical treatment if this is likely to have long-term benefits.	16.4% of men had received radiotherapy or a prostatectomy. This is lower than in SPARTAN reflecting the high proportion of men in TITAN who were newly diagnosed and such treatments may not be appropriate.

Patient Characteristic	ERG comment	
	SPARTAN	TITAN
Prior chemotherapy	A small proportion ([redacted]%) of men had received previous chemotherapy. Docetaxel is currently only recommended in newly diagnosed patients with high risk disease so this is less likely to have been used in patients who have progressed to hormone-resistant localised disease.	10.7% of men had received docetaxel chemotherapy. Clinical expert advice to the ERG is that chemotherapy is most often offered to younger, fitter men representing 30% of men with mHSPC.

Source: CS Tables 7 and 8; TITAN CSR Table 6 [23]

ERG conclusion

The two pivotal phase III RCTs, SPARTAN and TITAN, are appropriate study designs to inform the comparative effectiveness and safety of apalutamide plus ADT versus placebo plus ADT in this appraisal. Patients' baseline characteristics were well balanced between treatment arms in both studies and were considered to be broadly representative of patients with high-risk nmHRPC and mHSPC respectively. However, the ERG notes that the TITAN study population may be less representative of mHSPC patents who do not have bone disease and those patients who have primary disease progression.

3.2.2 Risk of bias assessment

The company reports quality assessments for the SPARTAN and TITAN trials, using the NICE recommended criteria, in Appendix D Tables D.55 and D.56 respectively, with a summary of both in CS B.2.5, including Table 11. The ERG's assessment of the trials, following the same criteria, is shown in Table 11 below. The criteria were applied by one ERG reviewer and checked by a second reviewer with differences in judgement resolved through discussion.

Table 11 Risk of bias assessment of the SPARTAN and TITAN trials

NICE criteria	SPARTAN		TITAN	
	Company	ERG	Company	ERG
Was randomisation carried out appropriately?	Yes	Agree	Yes	Agree
Was the concealment of treatment allocation adequate?	Yes	Agree	Yes	Agree
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Agree	Yes	Agree
Did groups receive same care other than intervention?	Yes	Agree	Yes	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation? Could this have impacted the outcome?	Yes	Agree[a]	Yes	Agree
Was there a clear definition of the outcome? Was the measure of this outcome valid/reliable?	Yes	Agree	Yes	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Agree[b]	No	Agree
Were there any unexpected imbalances in drop-outs between groups?	No	Agree	No	Agree
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Agree	Yes	Agree
Were there any other sources of bias	No	Agree	NR	Unclear
Whether the authors of the study publication declared any conflicts of interest?	NR	NR	Yes	Agree

Source: CS Appendix Tables 55 and 56 NR: Not reported in CS

[a] Blinded until patients were allowed to crossover from placebo to the apalutamide arm at the first interim data analysis.

[b] Except for HRQoL outcomes: CS Table 4 reports that SPARTAN HRQoL data are available from the final data analysis, however CS B.2.7.4 only reports data from the first data cut.

The ERG is in agreement with the company's judgements, with the following caveats:

- Blinding was only maintained for outcome data up to the first interim data analysis in SPARTAN. Thus, with the exception of MFS (which was intentionally only reported at the first interim data analysis), all outcomes reported at later data cuts will be at potential risk of detection bias and performance bias. These include survival endpoints such as PFS2 (which informs the economic model), though survival is more objectively measured compared to other outcomes, which may offset the increased risk of bias. The outcome data for TITAN reported in the CS is from the first data analysis, and is unaffected by the unblinding which occurred in that trial.

- Time to symptomatic progression data were reported in the CS only at the first SPARTAN interim data analysis, whereas CS Table 4 indicates that it was also measured at the final analysis, indicating potential selective reporting bias. The ERG notes that the results from the first interim analysis will not be affected by bias from unblinding, but those from the final analysis will.
- HRQoL outcome data for SPARTAN are reported in the CS using data from the first interim analysis, whereas CS Table 4 indicates that there is data available from the final analysis data cut in February 2020. Thus, there is potential for selective reporting bias.

As we have mentioned earlier (section 3.2.1.2) the crossover from placebo plus ADT to apalutamide plus ADT may potentially bias the ITT results at the final analysis in favour of placebo plus ADT. The higher use of NHS non-permitted subsequent novel therapy in the apalutamide plus ADT arm of the trial may over-estimate its effect in clinical practice. It may also counter the bias favouring placebo plus ADT arising from crossover. We discuss the company's choice of statistical methods to address bias from treatment switching later in this ERG report (section 3.2.4 (Trial statistical methods), and sections 4.2.6, 4.2.7 and 4.2.8 (Treatment effectiveness extrapolation methods)).

ERG conclusion

The ERG agrees that both SPARTAN and TITAN are of good methodological quality and could be considered low risk of bias on most of the bias-related criteria. Where SPARTAN reports outcomes subsequent to the first interim data analysis, the unblinding effect of the crossover from placebo plus ADT to the apalutamide plus ADT arm could increase the risk of performance bias and detection bias. Crossover may also confound survival estimates and therefore requires a suitable method to adjust the data analysis, something we discuss later in this report.

3.2.3 Outcomes assessment

3.2.3.1 Efficacy outcome(s)

The trial outcomes for SPARTAN and TITAN are defined in CS Table 6 and are listed below in Table 12. (Further information on these outcomes is provided in Appendix 9.1 of this report). In both trials, an appropriate range of intermediate- and longer-term endpoints have been included. All outcomes listed in the NICE scope have been included with the exception of 'response rate' which is not explicitly reported in SPARTAN, however, additional relevant supporting endpoints have been included.

Table 12 List of efficacy outcomes in SPARTAN and TITAN

Endpoint	SPARTAN[1]	TITAN
Primary/Co-primary	• Metastases-free survival (MFS)	• Radiographic progression-free survival (rPFS) • Overall survival (OS)
Secondary	• Overall survival (OS) • Time to metastases (TTM) • Progression-free survival (PFS) • Time to symptomatic progression • Time to initiation of chemotherapy	• Time to cytotoxic chemotherapy • Time to pain progression • Time to chronic opioid use • Time to skeletal-related events (SRE)
Other	• Second progression free survival (PFS2) • PSA response • Time to PSA progression	• Second progression free survival (PFS2) • Time to PSA progression • Overall response • Prostate cancer-specific survival

[1] Additional endpoints are reported in the trial CSR.

The efficacy endpoints were clearly defined and appropriate methods were used to minimise measurement bias by using an objective record e.g. documented prescription or medical event, blinded independent centralised review, audit of a sample of investigator-assessed outcomes and/or the use of standardised criteria for measuring response.

In SPARTAN, the primary endpoint of MFS is a relevant outcome for men with nmHRPC since progression to metastases may represent a turning point in the disease pathway as men become symptomatic and require further healthcare intervention. Clinical experts to the ERG advised that spending longer time without metastases would be of benefit to patients. MFS has been shown to correlate well with overall survival [27] We note, however, that it is possible that metastases may be detected in trial patients who may otherwise remain asymptomatic. The secondary endpoint, time to symptomatic progression, may be more relevant from a clinical management perspective. The ERG notes that the CS defines this secondary endpoint as a composite of three endpoints: skeletal-related events, pain

progression/worsening of symptoms or symptoms related to loco-regional progression requiring intervention. Data for these three individual components are not provided but may give more specific insight into the effect of apalutamide on symptoms, their management and associated resource use.

3.2.3.2 Efficacy outcomes informing the economic model

Efficacy data from SPARTAN for MFS, PFS2 and OS contributed to the economic model for nmHRPC. We consider these data to be mature as the planned event count was reached for MFS and median survival reached for both PFS2 and OS.

In TITAN, the choice of co-primary endpoints, rPFS and OS, secondary and additional clinically meaningful endpoints are relevant and have been appropriately measured. Efficacy data from TITAN for rPFS, PFS2 and OS inform the economic model for mHSPC but data for PFS2 and OS are currently immature.

3.2.3.3 HRQoL outcomes

Changes from baseline over time were measured for a number of well-established HRQoL measures based on patient-reported outcomes. In SPARTAN, two instruments were used:

- Generic: EuroQol-5-Dimensions 3 Levels (EQ-5D-3L) questionnaire and Visual Analogue Scale (EQ-VAS) and
- Disease-specific: Functional Assessment of Cancer Therapy–Prostate Cancer (FACT-P) questionnaire. FACT-P consists of a 27-item Functional Assessment of Cancer Therapy-General (FACT-G) with four dimensions (physical, social, emotional and functional well-being) and a 12-item prostate cancer specific scale. Items are rated on a Likert scale (from 0 to 4) and combined to produce a global score and domain-based subscale scores. A higher score represents better QoL.

In TITAN, in addition to the 5-level version of the EQ-5D and FACT-P, two other HRQoL instruments were used:

- Brief Fatigue Inventory (BFI) which measures cancer-related fatigue intensity and its interference on daily functioning. Numerical rating scales are scored from 0-11 with a higher score indicating worse fatigue.
- Brief Pain Index-Short Form (BPI-SF) which measures worst pain intensity, average pain and pain interference with daily functioning. Numerical rating scales are scored from 0-10 with a higher score indicating worse pain.

HRQoL was measured at various time points as shown in Table 13. The CS describes pre- and post-progression results for HRQoL (CS B.2.7.4 and Appendix L.1) for SPARTAN but only pre-progression results for TITAN (B.2.12.4 and Appendix L.2).

Table 13 Timing of assessment for HRQoL measures

HRQoL instrument	Timing of measurement	
	SPARTAN	TITAN
EQ-5D-3L/5L & EQ-VAS	At baseline, Day 1 of each 28-day cycle in cycles 2-6, then Day 1 of every two cycles in cycles 7-13, then Day 1 of every four cycles and every four months during long-term follow up until 12 months post-progression	At baseline, Day 1 of cycles 1-7, then every other cycle until end of treatment, and every four months for up to one year after discontinuation.
FACT-P		
BFI	Not measured	From Day -6 to Day 1 of each cycle visit until the end of treatment and every 4 months for up to a year after discontinuation.
BPI-SF	Not measured	

EQ-5D-3L: EuroQol 5-Dimension 3-Level VAS: Visual Analogue Scale
Source: CS Table 6, Table 21, Section B.12.4 and Agarwal et al. 2019.[20]

The ERG considers the range of general and disease-specific HRQoL outcomes in SPARTAN and TITAN to be appropriate to the respective patient populations. The additional measures used in TITAN reflect the need to assess the impact of treatment on pain and fatigue symptoms which are more relevant in patients with metastases.

3.2.3.4 Safety outcomes

Patients were assessed at each clinical visit for adverse events (AEs) and serious AEs. Treatment-emergent AEs were graded by severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 and coded at preferred term and system organ class level using Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1. Numbers of and reasons for dose changes, interruptions and discontinuations were also recorded. Trial investigators assessed relatedness of Aes to study treatment.

In SPARTAN, adverse events of special interest (AESI) included skin rash, fall, fracture, hypothyroidism and seizure. In response to clarification question A2, the company report that ischaemic heart disease was not a predefined AESI in either trial but emerged as a new AESI during the course of the TITAN trial and has thus been included in the results for SPARTAN in this submission and that this will be included in subsequent data cut(s) for TITAN.

ERG conclusion

We consider the efficacy, HRQoL and safety outcomes to be appropriate to the decision problem and scope. However, data on OS and PFS2 in TITAN (mHSPC) are currently immature.

3.2.4 Statistical methods of the included studies

Error! Reference source not found. provides a summary and ERG critique of the statistical methods used in the SPARTAN and TITAN trials.

Trial (patient group)	SPARTAN (nmHRPC)	TITAN (mHSPC)
Analysis populations		
	ITT population, defined as all randomised patients with study drug assignments designated according to initial randomization, regardless of whether patients receive study drug or receive a different drug (SPARTAN n=1,207; TITAN n=1,052). Safety population, defined as all randomised patients who received at least one dose of the study drug with treatment assignments designated according to actual study treatment received (SPARTAN n=1,201; TITAN n= 1,051).	
ERG comment:	Definition of ITT population accords with "true" ITT definition. Safety population as a proportion of the total number randomised was 99.5% (SPARTAN), and 99.9% (TITAN), thus minimal attrition bias.	
Sample size calculations		
	MFS (primary outcome) 372 events needed with 90% power to detect a 30% reduction in risk of metastases (HR = 0.70) for apalutamide plus ADT (two-sided α of 0.05).	rPFS (co-primary outcome) Approx ~368 rPFS events needed for at least 85% power to detect an HR of 0.67 (median rPFS of [redacted] months for ADT vs [redacted] months for apalutamide plus ADT) at a two-sided significance level of 0.005. OS (co-primary outcome) Approximately 410 events

	With an assumed median MFS of 25 months in the placebo plus ADT arm, the treatment effect would be an increase in median MFS of 11 months approx (25 to 36 months). Approximately 1,200 patients needed. (NB. The study was also powered for a decrease in risk of death, a secondary outcome)	required, with ~80% power to detect an HR of 0.75 (two tailed significance level of 0.045) with an assumed median OS of ** months for the ADT plus placebo group. Approximately 1,000 patients needed.
ERG comment:	Target sample size was reached in both trials, and therefore they can be considered sufficiently powered for their primary outcomes. The extension to median MFS in SPARTAN was greater than expected (25 months, versus 11 months, respectively). The median MFS in the placebo + ADT group was lower than expected (15.70 months versus 25 months). It is not clear why.	
Methods to account for multiplicty		
	[redacted] according to the pre-specified O'Brien-Fleming (OBF)-type alpha spending function with possible re-estimation of the required number of events necessary for the next analysis to maintain the desired conditional power. For change in EQ-5D-3L index score/VAS from baseline and least squares mean change from baseline in FACT-P and FACT-G total scores mixed models for repeated measures (MMRM)analyses were used which account for multiplicity.	Co-primary outcome rPFS was tested first at the two-sided 0.005 level of significance. If not statistically significant, the OS endpoint was to be tested at the two-sided 0.045 level of significance. Secondary endpoints were tested using a hierarchical sequence, in the order of presentation in CS section B.2.12.2 (secondary outcome results).
ERG comment:	The testing procedures specified appear to be appropriate to minimise misinterpretation due to multiple testing of outcomes.	
Analysis of outcomes		
	In both trials the analysis of outcomes was performed on the ITT population, incorporating the randomisation stratification factors (except where specified otherwise). The Kaplan-Meier method was used to summarise time-to-event outcomes. The Cox proportional-hazards model was used to estimate hazard ratios (with 95% CI)	

	Response endpoints summarised using descriptive statistics for categorical data by treatment group with the two treatment groups compared using the stratified Mantel-Haenszel test (except where expected counts in some cells are small then Fisher's exact test may be used). MFS, TTM and PFS based on BICR of radiographic tumour assessments data.	Endpoints with a binary outcome summarised by descriptive statistics for each treatment group. Treatment groups were compared using the chi-square test (except if expected counts in some cells are less than 5 when Fisher's exact test may be used). rPFS based on investigator assessed radiographic tumour assessments data.
ERG comment:	The analysis methods are considered appropriate for the outcome measures described.	
Handling of missing data		
	MFS: In the CS results are reported applying ex-US regulatory CHMP guidance. Patients without metastasis or death were censored on the date of the last tumour assessment (or date of randomisation if no tumour assessment had occurred since the baseline visit). Time of progression was determined using the first date with documented evidence of progression or death regardless of missed or unevaluable tumour assessments and regardless of any change in therapy. EQ-5D and FACT-P missing data handled as recommended in the User Manual's for these measures (and analysis by MMRM model).	[redacted]
ERG comment:	The approaches to handling missing MFS data are appropriate. The MMRM model is appropriate to account for missing HRQoL data over multiple time points.	Appropriate censoring rules were applied. There was no planned imputation for other missing or incomplete data.
Sensitivity & post-hoc analyses		
	For MFS and OS non-stratified log-rank tests were conducted as sensitivity analyses. For MFS, investigator assessed progression was conducted as a sensitivity analysis.	For rPFS and OS non-stratified log-rank tests were conducted as sensitivity analyses. For rPFS a sensitivity analysis was conducted based on central review data where the date of

	For OS, other sensitivity analyses were planned because a large number of subjects were expected to receive life-extending subsequent therapies.	progression was defined as the date of the scan showing 2 or more new bone lesions compared to the nadir of bone lesions (this was requested by the FDA). For OS other sensitivity analyses were planned to be carried out if deemed useful to interpret the result (adjusting for baseline prognostic factors, subsequent therapy use or cross-over)
ERG comment:	The sensitivity analyses described appear appropriate. No post-hoc analyses are described.	

BICR – blinded independent central review

3.2.4.1 Methods to adjust for the effects of treatment switching

The company use methods to adjust the survival estimates from both SPARTAN and TITAN RCTs to account for crossover from placebo plus ADT to apalutamide plus ADT when the trials were unblinded, and also to account for receipt of subsequent therapies not available/permitted in the NHS (to account for the one-novel-therapy-commissioning policy in England - the novel therapy analysis). The company explored the suitability of the statistical adjustments methods for treatment switching proposed in NICE DSU TSD 16:[28]

- Rank Preserving Structure Failure Time Models (RPSFTM)
- Iterative Parameter Estimation (IPE);
- Inverse Probability of Censoring Weights (IPCW);
- Two-stage method

After exploring the appropriateness of each of the above methods, the company chose to use an alternative method, which they describe as being a modification of RPSFTM using (external) patient-level data from COU-AA-302 an RCT comparing abiraterone acetate plus prednisone versus prednisone in metastatic castrate resistant prostate. The ERG's critique of the company's choice of adjustment method is provided in detail in section 4.2.6.2 of this report.

ERG conclusion

The company briefly summarise the statistical methods used in the SPARTAN and TITAN trials in the CS, with further detail given in the statistical analysis plans for these trials (sent in response to clarification question A9). The statistical methods appear appropriate for the aims and designs of the trials. The ERG did not identify any important limitations in the statistical analyses that would impact estimates of clinical effectiveness. The effects of crossover and the receipt of subsequent therapies not available in the NHS do impact clinical effectiveness and cost

effectiveness and the company has considered the available statistical adjustment methods recommended by NICE. The adjustment method they have chosen is similar to one of the NICE recommended methods with use of external data from an RCT. We provide a detailed critique of this in relation the modelling and extrapolation of survival data later in this report (Chapter 4).

3.2.5 Efficacy results for the high-risk nmHRPC population

In this section we focus on the three effectiveness outcomes that inform the economic model:

- MFS (primary outcome) in section 3.2.5.1
- OS (secondary outcome) in section 3.2.5.2
- PFS2 (other outcome) in section 3.2.5.3

We also present the OS and PFS2 results after adjustment for receipt of more than one novel therapy and patients who crossed over from the placebo plus ADT arm to the apalutamide plus ADT arm. We have not reported on effectiveness outcomes included in the CS that do not inform the economic model (time to initiation of cytotoxic chemotherapy; PSA response rate; time to PSA progression (TTPSA); and PSA kinetics in patients with advanced prostate cancer).

HRQoL outcomes (section 3.2.5.5), subgroup analyses (section 3.2.5.6) and safety outcomes (section 3.2.5.7) follow the effectiveness outcomes.

3.2.5.1 Primary outcome: Blinded independent central review (BICR) metastases-free survival (MFS)

BICR MFS was the primary outcome for the SPARTAN trial and the final analysis for this outcome took place at the first interim study analysis (clinical cut-off date 19th May 2017).

In the apalutamide plus ADT arm 209 patients (25.9%) had distant metastases or had died in comparison to 210 patients (52.4%) in the placebo plus ADT arm (Table 14). The majority of the BICR MFS events were metastases (Apalutamide plus ADT arm 204 metastases, placebo plus ADT arm 188 metastases) and Smith et al.[8] report that among the patients who had metastases, 60.5% in the apalutamide arm and 54.4% in the placebo arm had bone metastases.

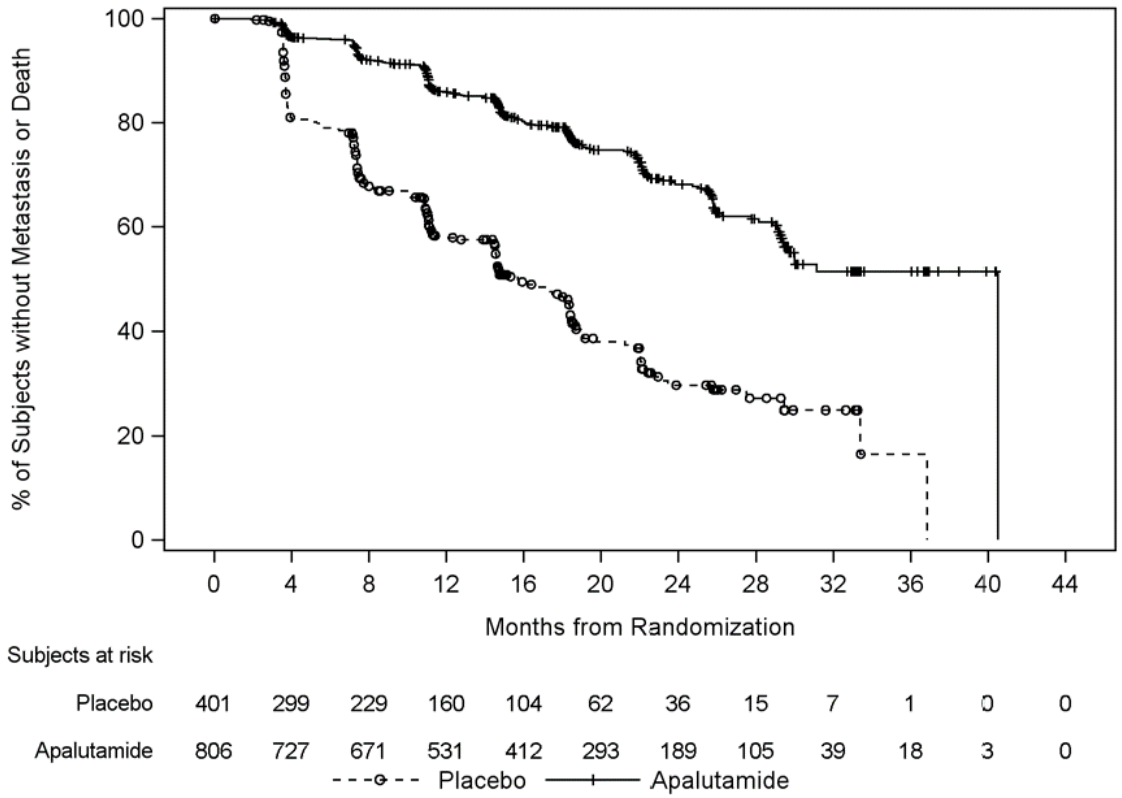
Median MFS was extended by 25 months from 15.70 months (95% CI: 14.55–18.40) for the placebo plus ADT arm to 40.51 months (95% CI: 29.70–40.51) for the apalutamide plus ADT

arm (Table 14). This is a statistically significant extension (p<0.0001) and our clinical experts agreed it is a clinically meaningful result.

Table 14 Summary of BICR MFS in SPARTAN (IA1, clinical cut-off date 19th May 2017; ITT population)

ITT population	Apalutamide plus ADT (n = 806)	Placebo plus ADT (n = 401)
Event, n (%)	209 (25.9)	210 (52.4)
Censored, n (%)	597 (74.1)	191 (47.6)
MFS (months)		
25th percentile (95% CI)	19.55 (18.23–22.14)	7.26 (5.55–7.43)
Median (95% CI)	40.51 (29.70–40.51)	15.70 (14.55–18.40)
75th percentile (95% CI)	40.51 (NE–NE)	29.47 (23.06–36.83)
Range	(0.0 [a]–40.5)	(0.0 [a]–36.8)
12-month event-free rate (95% CI)	0.861 (0.833–0.884)	0.579 (0.525–0.629)
24-month event-free rate (95% CI)	0.682 (0.638–0.722)	0.296 (0.235–0.360)
36-month event-free rate (95% CI)	0.514 (0.443–0.581)	0.165 (0.055–0.327)
p value	< 0.0001	
Hazard ratio (95% CI) [b]	0.297 (0.244–0.362)	

Source: CS Table 13
ADT: androgen deprivation therapy; BICR: blinded independent central review; MFS: metastases-free survival
[a] Censored observation.
[b] Hazard ratio is from a stratified proportional hazards model with a single factor of treatment group, stratified by PSADT (≤ 6 months vs > 6 months), bone-sparing agent use (yes vs no) and loco-regional disease (N0 vs N1). Hazard ratio < 1 favours active treatment.



Source: CS Figure 10
Notes: Analysis was performed with stratification according to PSADT (>6 months vs ≤6 months), use of bone-sparing agents (yes vs no), and classification of local or regional nodal disease (N0 vs N1) at the time of trial entry

Figure 3 Kaplan-Meier plot for BICR MFS in SPARTAN (IA1, clinical cut-off date 19th May 2017; ITT population)

3.2.5.2 Secondary outcome: Overall survival

At the final SPARTAN trial analysis (52 months median follow-up) there had been 274 deaths (34.0%) in the apalutamide plus ADT arm and 154 deaths (38.4%) in the placebo plus ADT arm (Table 15). The risk of death was decreased by 22% in the apalutamide plus ADT arm compared with placebo plus ADT (HR 0.784; 95% CI 0.643, 0.956), 2-sided p = 0.016). Median OS was extended in the apalutamide + ADT arm by 14 months (p<0.0001) to 73.9 months in the apalutamide plus ADT arm in comparison to 59.9 months in the placebo plus ADT arm (Table 15 and Figure 4).

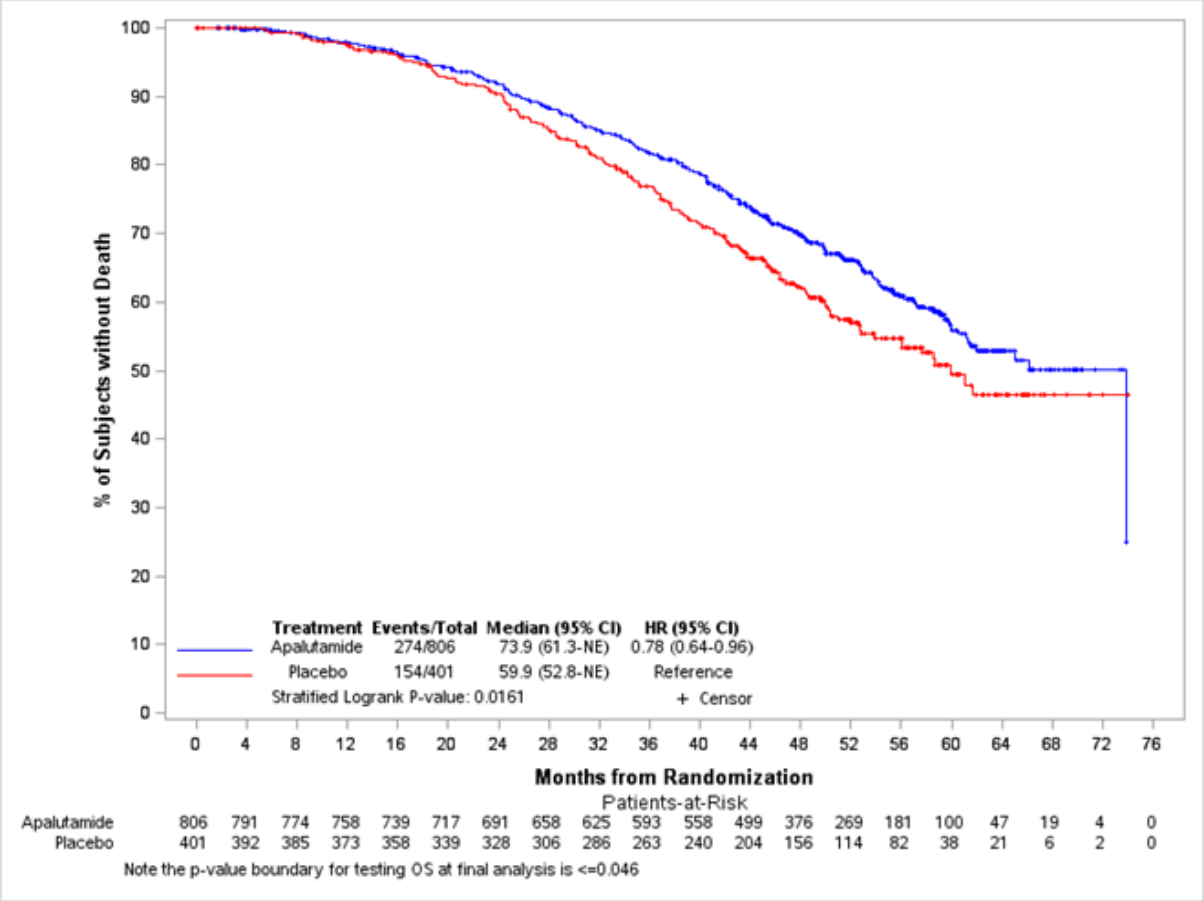
The company point out that statistically significant superiority of OS in the apalutamide plus ADT trial arm occurred despite any confounding that had occurred because of the patients who crossed over from placebo to apalutamide after the study was unblinded at the first interim analysis (n=76, which was 64% of the ongoing placebo plus ADT patients at unblinding, or 19.0% of randomised placebo plus ADT patients). Furthermore 279 (69.6%)

patients randomised to placebo plus ADT received life prolonging subsequent therapy for metastatic prostate cancer in comparison to 371 (46.0%) patients randomised to apalutamide plus ADT.

Table 15 Summary of OS in SPARTAN (Final analysis, clinical cut-off date 1st February 2020; ITT population)

ITT population	OS unadjusted for crossover	
	Apalutamide plus ADT (n = 806)	Placebo plus ADT (n = 401)
Event, n (%)	274 (34.0%)	154 (38.4%)
Censored, n (%)	[redacted]	[redacted]
OS (months)		
25th percentile (95% CI)	[redacted]	[redacted]
Median (95% CI)	73.86 (61.21–NE)	59.89 (52.80–NE)
75th percentile (95% CI)	[redacted]	[redacted]
Range	[redacted]	[redacted]
1-year survival rate (95% CI)	[redacted]	[redacted]
2-year survival rate (95% CI)	[redacted]	[redacted]
3-year survival rate (95% CI)	[redacted]	[redacted]
4-year survival rate (95% CI)	[redacted]	[redacted]
5-year survival rate (95% CI)	[redacted]	[redacted]
6-year survival rate (95% CI)	[redacted]	[redacted]
p value	0.0161	
Hazard ratio (95% CI) [b]	0.784 (0.643–0.956)	

Source: CS Table 14
ADT: androgen deprivation therapy; OS: overall survival
[a] Censored observation
[b] Hazard ratio is from a stratified proportional hazards model with a single factor of treatment group, stratified by PSADT (≤ 6 months vs > 6 months), bone-sparing agent use (yes vs no) and loco-regional disease (N0 vs N1). Hazard ratio < 1 favours active treatment.

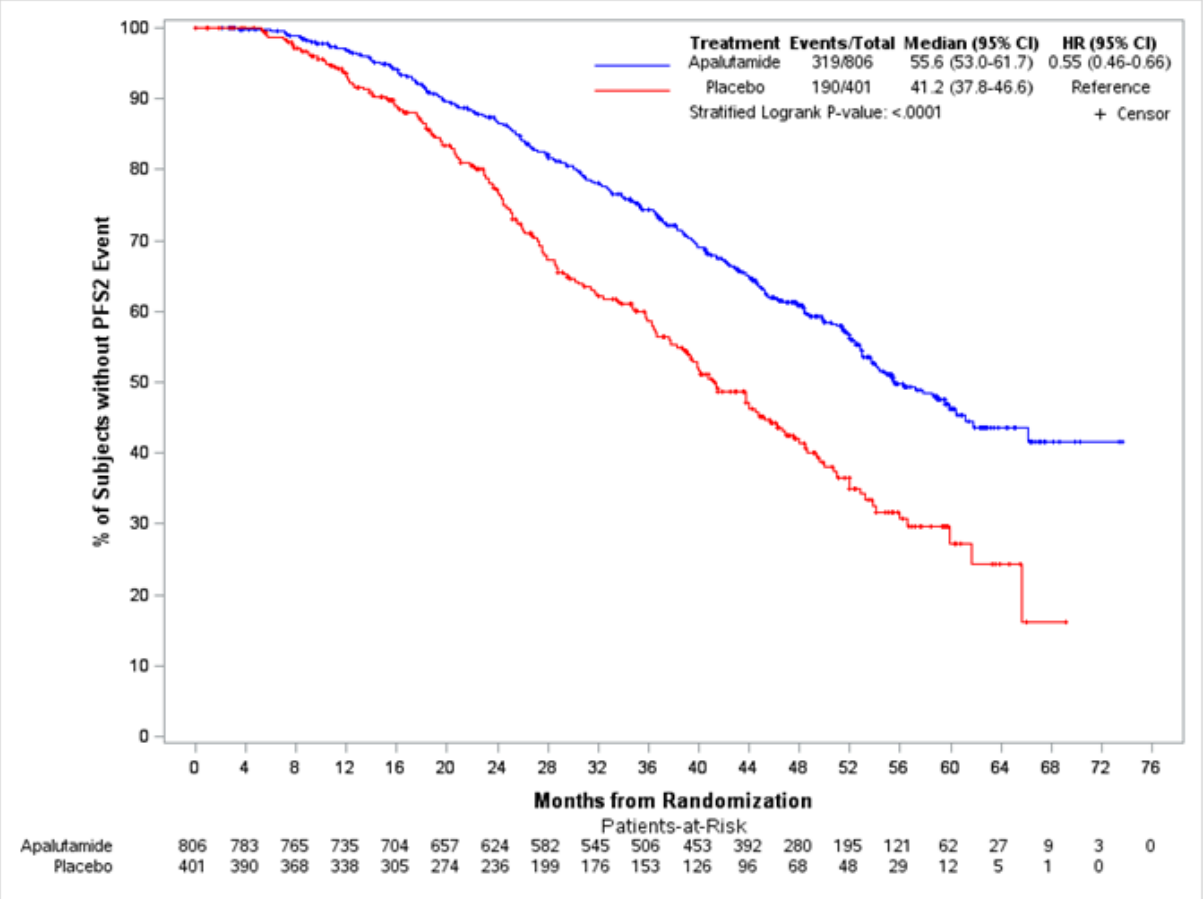


Source: CS Figure 11
NE, not estimable

Figure 4 Kaplan-Meier plot for OS in SPARTAN (Final analysis, clinical cut-off date 1st February 2020; ITT population)

3.2.5.3 Second progression-free survival (PFS2)

In the apalutamide plus ADT arm there was a statistically significant extension in PFS 2 of 14.4 months in comparison to the placebo plus ADT arm in the SPARTAN RCT (p<0.0001). In the apalutamide plus ADT arm 319 (39.6%) participants had a PFS2 event in comparison to 190 (47.4%) in the placebo plus ADT arm. The risk of a PFS2 event was decreased by 45% in the apalutamide plus ADT arm compared with placebo plus ADT (HR 0.55; 95% CI 0.46 to 0.66, p < 0.0001).



Source: CS Figure 12
NE: not estimable

Figure 5 Kaplan-Meier plot for PFS2 (SPARTAN, Final analysis, clinical cut-off date 1st February 2020; ITT population)

3.2.5.4 Adjustment of OS and PFS2

As already described earlier in this report (section 3.2) patients randomised to placebo plus ADT were permitted to crossover to receive apalutamide plus ADT after trial unblinding, and 19% of placebo plus ADT arm participants crossed over. Additionally, some patients in SPARTAN received subsequent treatment with therapies that are not available in English clinical practice, and some patients who received apalutamide also received one or more additional novel therapies (abiraterone and enzalutamide) [apalutamide plus ADT arm [redacted] received a second novel therapy in comparison to [redacted] in the placebo + ADT arm). In contrast, in England patients are only permitted to receive one novel therapy (i.e. if they had already received apalutamide they would not be permitted to receive abiraterone or enzalutamide). The CS summarises the life-prolonging subsequent therapies received in SPARTAN in CS Table 16.

The company used a modified RPSFTM approach, as described by Diels et al[29] to adjust the results for the effects of i) receiving more than one novel therapy during the course of their disease and ii) the crossover from the placebo plus ADT arm to the apalutamide plus ADT arm. Further detail on the adjustment methods can be found in section 4.2.6, 4.2.7 and 4.2.8 of this report. The adjusted results are shown alongside the unadjusted results in Table 16.

Table 16 Comparison of unadjusted OS and PFS2 with adjusted OS and PFS2 results from SPARTAN

ITT population	Unadjusted	Adjusted
OS: Hazard ratio (95% CI)	0.784 (0.643 to 0.956) p = 0.0161	0.77 (0.64 to 0.94) p-value not reported
PFS2: Hazard ratio (95% CI)	[redacted]	[redacted] p-value not reported

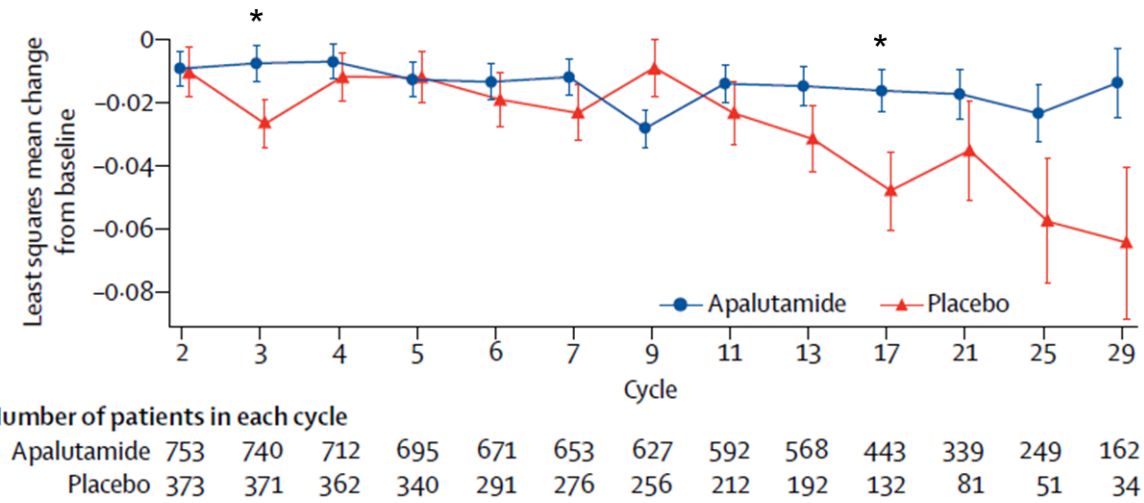
Source: CS Tables 14 and 15, supplemented with information from CS p. 78-79.

3.2.5.5 HRQoL outcomes

Two questionnaires were used to collect HRQoL data at pre-progression and post-progression disease stages; the EQ-5D-3L and the FACT-P. Further detail on how data from these outcomes were used in the economic model is provided in section 4.2.10 of this report. The company do not report on the HRQoL results in the post-progression phase in the main CS report (the data are presented in CS appendix L) and these data are not presented in this section.

3.2.5.5.1 EQ-5D-3L

Figure 6 shows the EQ-5D-3L scores were comparable across both treatment arms and HRQoL was maintained in patients who received apalutamide plus ADT. Although the mean changes in EQ-5D-3L index scores were suggestive of a decline in HRQoL in the placebo arm, particularly from cycle 11 onward, a statistically significant difference between trial arms was only observed at two time points (cycle 3 and cycle 17).



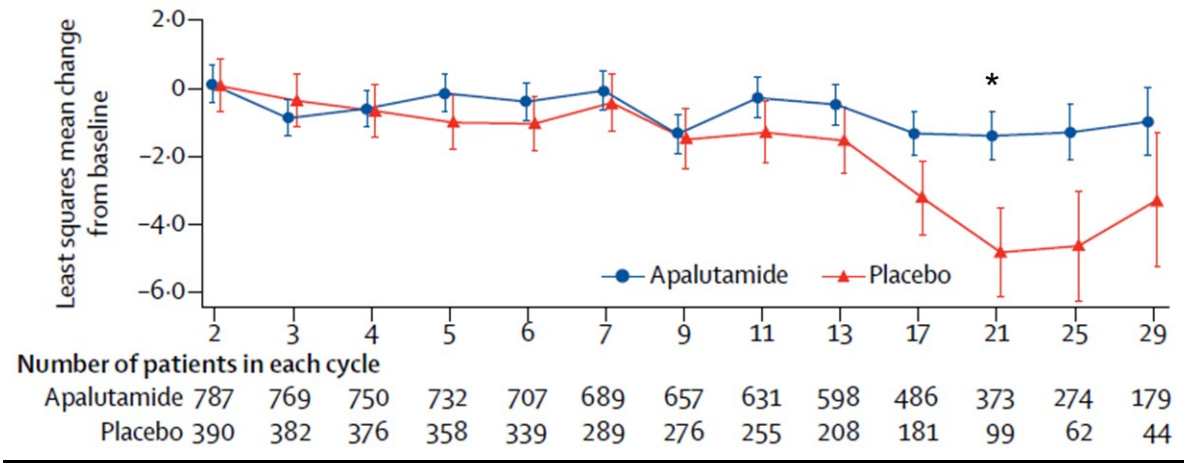
Number of patients in each cycle													
Apalutamide	753	740	712	695	671	653	627	592	568	443	339	249	162
Placebo	373	371	362	340	291	276	256	212	192	132	81	51	34

Source: CS Figure 16
Notes: * indicates $p < 0.05$. Note that the x axis intervals are not constant

Figure 6 Least squares mean change in EQ-5D-3L index score pre-progression from baseline (repeated measures analysis) in SPARTAN (IA1; clinical cut-off date 19th May 2017; ITT population)

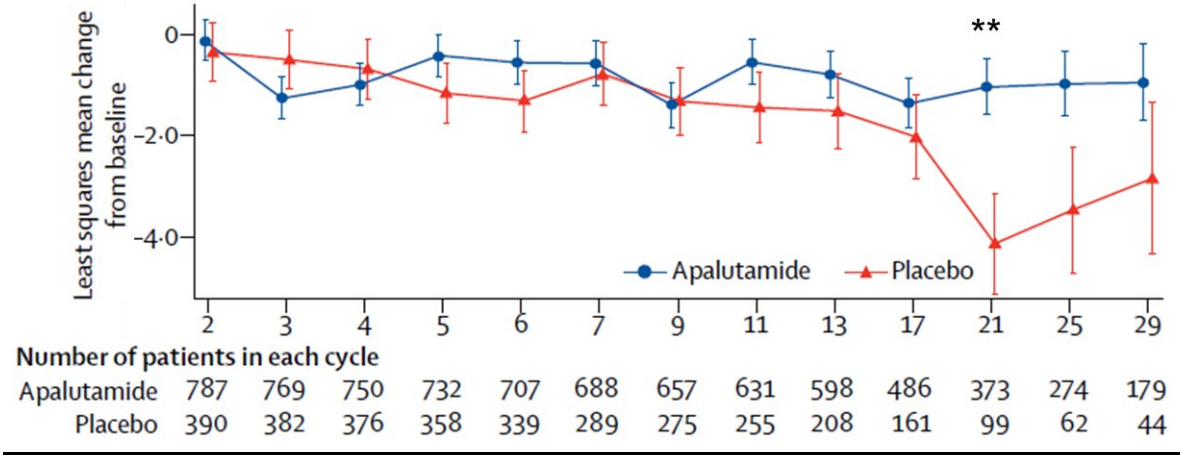
3.2.5.5.2 FACT-P

The FACT-P (which consists of the FACT-G and a 12-item prostate-specific scale) results were in line with the EQ-5D-3L results. The least squares mean changes from baseline to cycle 29 of treatment in FACT-P scores and FACT-G scores are shown in Figure 7 and Figure 8 respectively. Completion of the FACT-P questionnaire was at least 95% (range 95% to 100%) at any assessment visit and the company states the completion rates were similar between the treatment arms. At baseline the FACT-P and FACT-G scores were similar in the two treatment arms and HRQoL was maintained in patients who received apalutamide plus ADT (Figure 7 and Figure 8 respectively). In line with the EQ-5D-3L results, the FACT-P and FACT-G data were suggestive a decline in HRQoL in the placebo arm in later treatment cycles (from about cycle 11). However, statistically significant differences between trial arms were observed at cycle 21 only.



Source: CS Figure 18, ERG has deleted some abbreviations
FACT-P: Functional Assessment of Cancer Therapy – Prostate
Notes: * indicates $p < 0.05$. Note that the x axis intervals are not constant

Figure 7 Least squares mean change from baseline in FACT-P total scores (repeated measures analysis) in SPARTAN (IA1; clinical cut-off date 19th May 2017; ITT population)



Source: CS Figure 19, ERG has deleted some abbreviations
FACT-G: Functional Assessment of Cancer Therapy – General
Notes: * indicates $p < 0.05$. Note that the x axis intervals are not constant

Figure 8 Least squares mean change from baseline in FACT-G total scores (repeated measures analysis) in SPARTAN (IA1; clinical cut-off date 19th May 2017; ITT population)

3.2.5.6 Subgroup analyses

For the nmHRPC population the NICE scope did not list any particular subgroup of interest.

The company conducted analyses for the nmHRPC population on the outcomes of MFS and OS across a range of pre-defined subgroups as shown in CS Figure 20 and Figure 21 respectively.

For MFS, the results favoured apalutamide plus ADT over placebo plus ADT in all subgroups except that for black adults. However, the sample size for this subgroup was small (n=68) therefore the result is subject to uncertainty as evidenced by the wide confidence intervals for the hazard ratio (HR 0.59, 95% CI 0.23 to 1.48).

For OS, the results favoured apalutamide plus ADT over placebo plus ADT in the majority of subgroups with three exceptions. The first exception was in the subgroup of adults aged 65 to less than 75 years where the HR of 1.02 (95% CI 0.74 to 1.42) differed from the other two age subgroups (<65 years HR of 0.39, 95% CI 0.19 to 0.78) and ≥75 years HR of 0.74, 95% CI 0.57 to 10.97). The CS states there seems to be no clinical rationale why the middle of the three age subgroups should differ in response to apalutamide plus ADT in comparison to the other two age subgroups. The other two exceptions were the subgroups of Black (HR 1.11, 95% CI 0.40 to 3.09, n=68) and of Asian (HR 1.22, 95% CI 0.58 to 2.53, n=140) patients. The company suggests that the hazard ratios observed may have been due to a combination of the small sample sizes, few death events and differences between the treatment arms of these two subgroups.

3.2.5.7 Safety outcomes

The company's safety analysis includes [redacted] 803 patients in the apalutamide plus ADT arm and 398 patients in the placebo arm.

3.2.5.7.1 Treatment duration, dose interruptions and dose modifications

There was a significant difference in the median exposure to treatment between the two treatment arms (apalutamide plus ADT median of 32.9 months versus placebo plus ADT median of 11.5 months, CS Figure 22 and cumulative exposure to study treatments summarised in CS Table 22). There were still [redacted] of patients in the apalutamide plus ADT arm still on treatment at [redacted] at the final analysis whereas there were only [redacted] patients still on treatment at [redacted] in the placebo plus ADT arm. The CS therefore presents and discusses TEAE incidence in terms of events per 100 patient-years when appropriate to take account of the difference in median exposure between the two arms.

Most patients in both study arms were able to tolerate the full prescribed dose of study medication and most received no dose modifications (no dose modifications in [redacted] of the apalutamide plus ADT arm and [redacted] of the placebo plus ADT arm). The CS summarises the reasons for the dose reductions and interruptions that were necessary in CS Table 23.

3.2.5.7.2 Summary of adverse events

The company's summary table of adverse events is reproduced below in Table 17.

Table 17 Summary of adverse events SPARTAN trial (Final analysis; clinical cut-off date 1st February 2020; safety population

AE, n (%)	Apalutamide plus ADT (n = 803)		Placebo plus ADT (n = 398)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
All causality Aes	781 (97.3%)	449 (55.9%)	371 (93.2)	373 (93.7%)
Drug-related Aes [a]	[redacted]	[redacted]	[redacted]	[redacted]
Aes leading to treatment discontinuation	120 (14.9%)	[redacted]	29 (7.3%)	[redacted]
Drug-related Aes leading to treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
All-causality SAEs [b]	290 (36.1%)	[redacted]	99 (24.9%)	[redacted]
Drug-related SAEs[a]	[redacted]	[redacted]	[redacted]	[redacted]
Fatal SAEs	24 (3.0%)	[redacted]	2 (0.5%)	-
Fatal drug-related SAEs[a]	1 (0.1%)	[redacted]	[redacted]	[redacted]

Source: reproduction of CS Table 24, footnotes edited.
AE: adverse event; SAE: serious adverse event
[a] Adverse events reported as related. [b] Excludes Grade 5.
Notes: Percentages are based on the Safety population. For each category patients are counted only once even if they experienced multiple events in that category.

3.2.5.7.3 Summary of treatment emergent adverse events

The company summarised the TEAEs that occurred in more than 15% of patients in either study arm. The company's summary table is reproduced below with events ordered by the proportion in the apalutamide plus ADT arm experiencing that event (any grade).

Table 18 Summary of most frequent all-causality treatment-emergent adverse events reported in > 15% patients in SPARTAN (Final analysis; clinical cut-off date 1st February 2020; safety population)

	Apalutamide plus ADT (n = 803)		Placebo plus ADT (n = 398)	
AE (%)[a]	**Any grade**	**Grade 3-4**	**Any grade**	**Grade 3-4**
Fatigue	262 (32.6%)	7 (0.9%)	85 (21.4%)	1 (0.3%)
Hypertension	225 (28.0%)	131 (16.3%)	83 (20.9%)	49 (12.3%)
Diarrhoea	187 (23.3%)	12 (1.5%)	61 (15.3%)	2 (0.5%)
Arthralgia	160 (19.9%)	3 (0.4%)	33 (8.3%)	0
Nausea	157 (19.6%)	0	63 (15.8%)	0
Weight decreased	157 (19.6%)	12 (1.5%)	26 (6.5%)	1 (0.3 %)
Back pain	144 (17.9%)	11 (1.4%)	61 (15.3%)	6 (1.5%)
Hot flush	122 (15.2%)	0	34 (8.5%)	0

Source: CS Table 25, duplicate row for nausea deleted, rows reordered, footnotes edited.
[a] Treatment-emergent Aes were those that occurred between the date of 1st dose of study drug and date of last dose of study drug +28 days
Notes: Patients are counted only once for any given event, regardless of the number of times they experienced the event. The event experienced by the patient with the worst toxicity grade is used. If a patient had all Aes with missing toxicity grades, the patient is only counted in the "All grades" column

Grade 3 and 4 adverse events

The company summarise treatment-emergent grade 3 and grade 4 Aes (reported in 5% or more of patients) in CS Table 26. A greater proportion of patients in the apalutamide plus ADT arm experienced grade 3-4 TEAEs than in the placebo plus ADT arm (56% versus 36% respectively) with grade 3 events being more common than grade 4 events ([redacted] of patients in the apalutamide plus ADT arm and [redacted] of patients in the placebo plus ADT arm.

However, after adjustment for the longer exposure time for the apalutamide plus ADT arm the Grade 3 and Grade 4 TEAE rates were lower in the apalutamide plus ADT arm than in the placebo plus ADT arm (Grade 3: [redacted] events per 100 patient-years in the apalutamide plus ADT arm in comparison to [redacted] for the placebo arm; Grade 4: [redacted] events per 100 patient-years in the apalutamide plus ADT arm in comparison to [redacted] for the placebo arm. The results adjusted for exposure time to study treatments indicate that the addition of apalutamide to ADT was not associated with an additional incidence of grade 3 and grade 4 TEAEs.

3.2.5.7.4 Summary of serious adverse events

The most frequent treatment-emergent SAEs (reported in 1% or more of patients) are summarised in CS Table 27. A greater proportion of patients in the apalutamide plus ADT arm experienced an SAE than in the placebo plus ADT arm (36% versus 25% respectively).

After adjustment for the longer exposure time for the apalutamide plus ADT arm the number of distinct treatment-emergent SAEs was lower in the apalutamide plus ADT arm than in the placebo plus ADT arm (13.7 events per 100 patient-years in the apalutamide plus ADT arm in comparison to 22.2 for the placebo arm. The company adjusted the frequently reported SAEs (occurring in at least 1% of patients) and found that the SAE profiles were similar for both trial arms (Table 19).

Table 19 Treatment-emergent SAEs adjusted for treatment exposure

	Apalutamide plus ADT (n=803)	**Placebo plus ADT (n=398)**
Treatment-emergent SAEs per 100 patient-years	13.7	22.2
Frequently reported SAEs[a], that occurred at a higher incidence in the APA+ADT arm than the placebo arm, adjusted for exposure		
Pneumonia	[redacted]	[redacted]
Fall	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Cerebrovascular accident	[redacted]	[redacted]
Syncope	0.3	0.2
Osteoarthritis	0.3	0
Haematuria	0.6	0.7
Urinary tract infection	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]
Urinary retention	[redacted]	[redacted]
Hydronephrosis	[redacted]	[redacted]
Urinary tract obstruction	[redacted]	[redacted]
[a] Occurring in at least 1% of patients		

3.2.5.7.5 Summary of adverse events of special interest

A summary of treatment-emergent adverse events of special interest (AESI) is presented in CS Table 28. These results are not adjusted for treatment exposure. The incidence of AESI was higher for all the events (skin rash, fall, fracture, hypothyroidism, ischaemic heart disease and seizure) in the apalutamide plus ADT arm than in the placebo plus ADT arm. Overall, [redacted] of the apalutamide arm experienced an AESI compared to [redacted] of the placebo plus ADT arm. The biggest difference between arms in a single AESI was for skin rash (26.4% of the apalutamide arm compared to 6.3% of the placebo plus ADT arm). Our clinical experts highlighted the importance of adjusting for treatment exposure and suggested falls, seizures and cardiac events warranted further consideration. This information is provided in the SPARTAN CSR[17] which reports:

- The incidence of fall is still higher in apalutamide arm after adjustment for treatment exposure (12.4 events per 100-person years vs 9.6 events in the placebo arm)
- Seizures, which occurred only in the apalutamide arm, are a rare event (0.2 events per 100-patient years) and the exposure adjusted incidence suggests the risk does not diminish over time on apalutamide therapy
- [redacted]

3.2.5.7.6 Summary adverse events leading to death

The company's summary table of adverse events leading to death is reproduced below (Table 20). The data have not been adjusted for treatment exposure. A greater proportion of participants in the apalutamide plus ADT arm died within 28 days of the last dose of study medication due to an adverse event (2.2% of the apalutamide arm compared to 0.5% of the placebo plus ADT arm).

Table 20 Summary of deaths (SPARTAN, safety population)

	Apalutamide plus ADT (n = 803)	**Placebo plus ADT (n = 398)**
Number of patients with TEAEs leading to death n (%)	24 (3)	2 (0.5)
Drug related[a]	1 (0.1)	0
All deaths within 28 days of last dose	22 (2.7)	2 (0.5)
Adverse event	18 (2.2)	2 (0.5)

	Apalutamide plus ADT (n = 803)	Placebo plus ADT (n = 398)
Death due to prostate cancer	3 (0.4)	0
Other	1 (0.1)	0

Source: CS Table 29, footnotes edited.
[a] adverse events reported as related
Notes: Percentages are based on the safety population. TEAEs are those that occurred between the date of first dose of study drug and date of last dose of study drug +28 days. For each category, subjects are counted only once, even if the experienced multiple events in that category

3.2.6 Efficacy results for the mHSPC population

In this section we focus on the three effectiveness outcomes that contribute data to the economic model:

- rPFS (co-primary outcome) in section 3.2.6.1
- OS (co-primary outcome) in section 3.2.6.2
- PFS2 (other outcome) in section 3.2.6.3

We also present the OS and PFS2 results after adjustment for patients who received more than one novel therapy. We do not report on effectiveness outcomes included in the CS that do not inform the economic model. These outcomes are: time to initiation of cytotoxic chemotherapy; time to pain progression; time to opioid use; time to SREs; time to PSA progression; best overall response; prostate cancer-specific survival; and time to symptomatic local progression.

HRQoL outcomes (section 3.2.6.5), subgroup analyses (section 3.2.6.6) and safety outcomes (section 3.2.6.7) follow the effectiveness outcomes.

3.2.6.1 Co-primary outcome: radiographic progression-free survival (rPFS)

rPFS (assessed by investigator) was a co-primary outcome for the TITAN RCT with all scans collected for blinded independent review (although only about 60% we subject to independent central review). At the time of the primary analysis (clinical cut-off date 23rd November 2018) a stratified log-rank test showed rPFS was statistically significantly delayed in the apalutamide plus ADT arm in comparison to the placebo plus ADT arm (HR 0.48, 95% CI 0.39 to 0.60, p<0.0001) (Table 21). A sensitivity analysis using a non-stratified log rank test confirmed this result (HR 0.49, 95% CI 0.40 to 0.61, p<0.0001) as did supportive analyses using a multivariate Cox regression analysis (HR 0.43, 95% CI 0.34 to 0.54, p<0.0001). In response to clarification question A1 the company provided the results from the BICR analysis of rPFS. These results, from a random sample of approximately 60% of

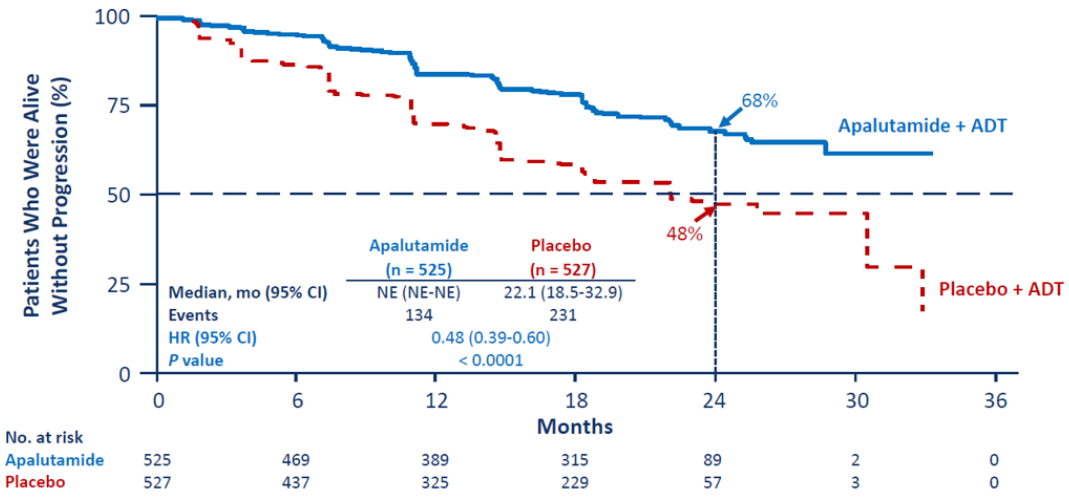
TITAN participants were in line with the investigator assessed results (HR [redacted]).

In the apalutamide plus ADT arm 134 of the ITT population (25.5%) experienced an rPFS event in comparison to 231 (43.8%) of the placebo plus ADT arm. Median rPFS was not reached in the apalutamide +ADT arm and was 22 months in the placebo plus ADT arm (Figure 9).

Table 21 Summary of rPFS in TITAN (investigator assessed, ITT population).

ITT population	Apalutamide plus ADT (n = 525)	Placebo plus ADT (n = 527)
Event, n (%)	134 (25.5)	231 (43.8)
Censored, n (%)	391 (74.5)	296 (56.2)
rPFS (months)		
25th percentile (95% CI)	18.43 (17.38, 22.11)	10.91 (8.71, 11.10)
Median (95% CI)	NE (NE, NE)	22.08 (18.46, 32.92)
75th percentile (95% CI)	NE (NE, NE)	32.92 (30.49, NE)
Range	(0.0[a], 33.3[a])	(0.0[a], 33.1[a])
62-month event-free rate (95% CI)	0.955 (0.932, 0.970)	0.870 (0.838, 0.896)
12-month event-free rate (95% CI)	0.843 (0.807, 0.873)	0.703 (0.660, 0.741)
24-month event-free rate (95% CI)	0.682 (0.629, 0.729)	0.475 (0.421, 0.528)
36-month event-free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p value [b]	< 0.0001	
Hazard ratio (95% CI) [c]	0.484 (0.391, 0.600)	

Source: CS Table 31
ADT: androgen deprivation therapy; rPFS: radiographic progression-free survival
[a] censored observation. [b] p-value is from the log-rank test stratified by Gleason score at diagnosis (≤ 7 vs >7, Region (NA/EU vs Other Countries) and Prior docetaxel use (Yes vs No). [c] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favours active treatment.



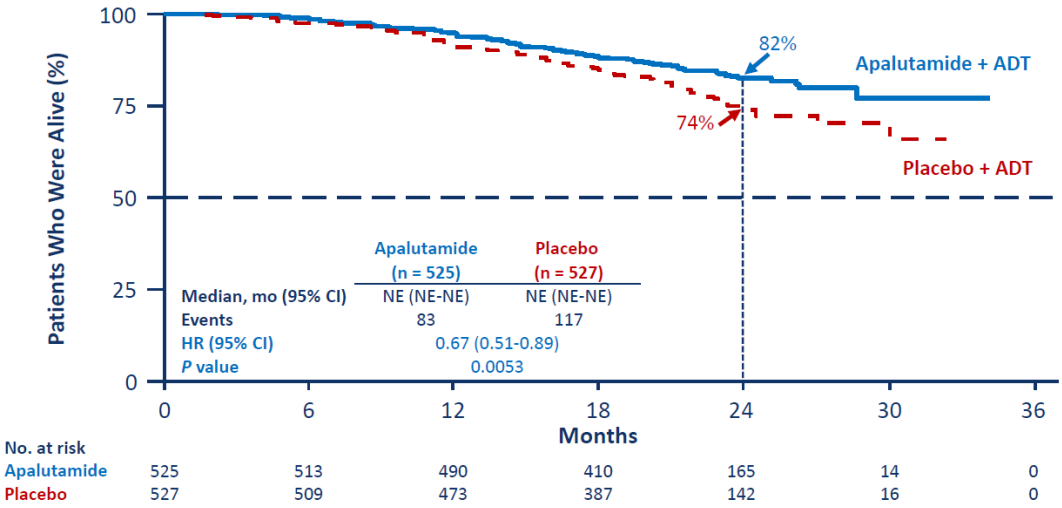
Source: CS Figure 23
NE: not estimable

Figure 9 Kaplan-Meier plot of rPFS (TITAN, ITT population)

3.2.6.2 Co-primary outcome: Overall survival

At the first interim TITAN trial analysis (clinical cut-off date 23rd November 2018, 22 months follow-up) there had been 83 deaths (15.8%) in the apalutamide plus ADT arm and 117 deaths (22.2%) in the placebo plus ADT arm. The risk of death was decreased by 33% in the apalutamide plus ADT arm compared with placebo plus ADT (HR 0.67; 95% CI 0.51 to 0.89, p = 0.0053). Median OS was not reached in either arm (Figure 10).

Results from the sensitivity analysis using a non-stratified log-rank test for OS (HR [redacted]) support those from the stratified log-rank test. Similarly, the results from a supportive analysis using a multivariate Cox regression analysis are consistent with the primary analysis (HR [redacted]).

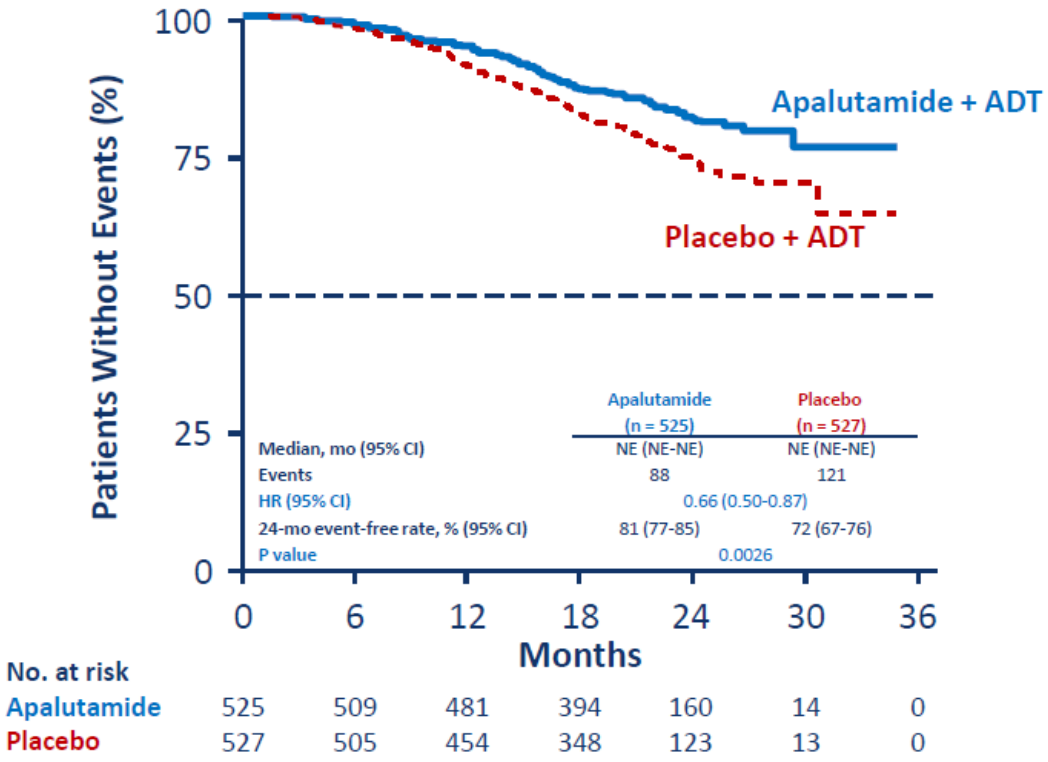


Source: CS Figure 24
NE: not estimable

Figure 10 Kaplan-Meier plot of OS (TITAN, ITT population)

3.2.6.3 PFS2

PFS 2 was statistically significantly delayed in the apalutamide plus ADT arm in comparison to the placebo plus ADT arm in the TITAN RCT. In the apalutamide plus ADT arm 88 (16.8%) participants had a PFS2 event in comparison to 121 (23.0%) in the placebo plus ADT arm. Median time to PFS 2 was not reached in either arm (Figure 11). The risk of a PFS2 event was decreased by 34% in the apalutamide plus ADT arm compared with placebo plus ADT (HR 0.66; 95% CI 0.50 to 0.87, p = 0.0026).



Source: CS Figure 25
NE: not estimable

Figure 11 Kaplan-Meier plot of time to PFS2 (TITAN, ITT population)

3.2.6.4 Adjustment of OS and PFS2

As already described earlier in this report (section 3.2), patients randomised to placebo plus ADT in the TITAN trial were permitted to crossover to receive apalutamide plus ADT after trial unblinding. Data for the trial period after unblinding and crossover is not yet available hence the OS and PFS2 data included in the CS are unaffected by confounding due to crossover. However, similarly to the SPARTAN trial, some patients in TITAN received subsequent treatment with therapies that are not available in English clinical practice, with some patients in particular receiving more than one novel therapy [apalutamide plus ADT arm [redacted] received a second novel therapy in comparison to [redacted] in the placebo + ADT arm). The CS summarises the life-prolonging subsequent therapies received in TITAN in CS Table 132.

The company used a modified version of the RPSFTM[29] and inverse probability of censored weights (IPCW) methodologies to adjust the results for the effects of patients receiving more than one novel therapy during the course of their disease. Further detail on the adjustment

methods can be found in sections 4.2.6, 4.2.7 and 4.2.8 of this report. The adjusted results are shown alongside the unadjusted results in Table 22.

For OS, both the RPSFTM and IPCW methods of adjustment had very limited impact. For PFS2 adjustment using the RPSFTM method had very limited impact. For the IPCW adjustment of PFS2 the company states that the results were counterintuitive since they did not fit with the clinical hypothesis of these analyses (i.e. the adjusted HR suggested increased benefit whereas the hypothesis was the adjustment should lower the benefit). The IPCW-adjusted PFS2 results were therefore not carried over to the cost-effectiveness modelling.

Table 22 Comparison of unadjusted OS and PFS2 with adjusted OS and PFS2 results from TITAN

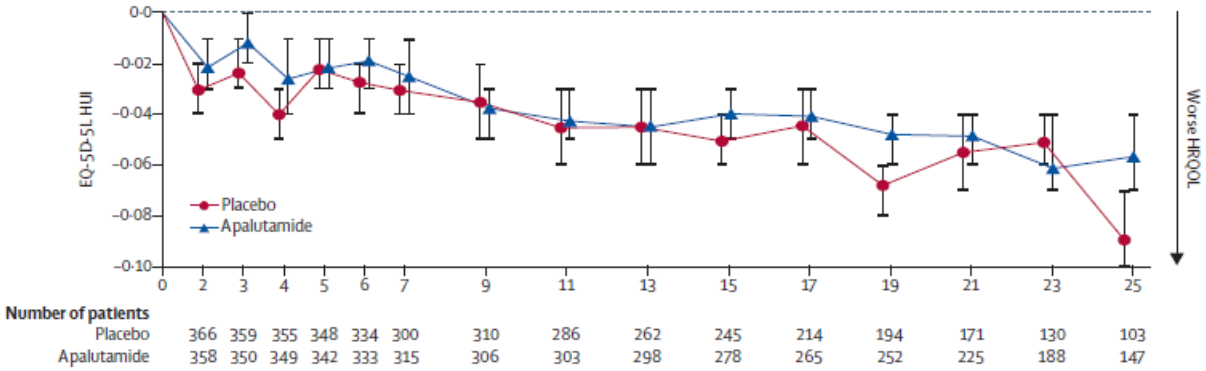
ITT population	Unadjusted	Adjusted – RPSFTM	Adjusted – IPCW
OS: HR (95% CI)	0.67 (0.51 to 0.89) p = 0.0053	0.67 (0.51 to 0.89)	0.67 (0.49 to 0.92)
PFS2: HR (95% CI)	0.66 (0.50 to 0.87) p = 0.0026	0.66 (0.51 to 0.87)	0.62 (0.46 to 0.83)

3.2.6.5 HRQoL outcomes

Four questionnaires were used to collect HRQoL over time from mHSPC participants in the TITAN RCT: the EQ-5D-5L, the FACT-P, the BFI and the BPI-SF. Further detail on how data from these outcomes were used in the economic model is provided in this report, section 4.2.10. Although HRQoL outcomes were collected in the TITAN RCT during treatment (37 cycles) and at the 4-, 8- and 12-month follow-ups, the data presented by the company in CS section B.2.12.4 are for the first 25 (EQ-5D-5L and FACT-P) or first 29 (BPI-SF and BFI) 28-day treatment cycles only.

3.2.6.5.1 EQ-5D-5L

The company present data which show there are no statistically significant differences between trial arms during treatment in the mean change from baseline in EQ-5D-5L VAS scores (CS Figure 28) or the EQ-5D-5L index scores (Figure 12 below).



Source: CS Figure 29, ERG has deleted some abbreviations
MMRM: mixed models for repeated measures

Figure 12 Mean change in EQ-5D-5L index score from baseline (MMRM; TITAN, ITT population)

3.2.6.5.2 BPI-SF

At baseline most patients either reported no pain (38%) or mild pain (38%). The MMRM analysis of mean changes in BPI-SF scores from baseline showed that mean changes were similar between the treatment arms of the trial and treatment with apalutamide plus ADT did not increase worst pain intensity (CS Figure 30) or pain interference (CS Figure 31) from baseline. The company also report that median time to worst pain intensity progression was 19.1 months in the apalutamide plus ADT arm versus 12.0 months in the placebo plus ADT arm. Median time to pain interference progression was not reached in either arm.

3.2.6.5.3 BFI fatigue scores

During 29 treatment cycles BFI fatigue scores in both trial arms remained stable for both worst fatigue intensity and for fatigue interference. The mean changes from baseline in BFI scores were similar between treatment arms (CS Figure 32 and 33).

3.2.6.5.4 FACT-P and FACT-G scores

FACT-P group mean total scores for HRQoL were maintained from baseline to the end of treatment (scores stated to be similar in both groups at baseline but data not presented). Additionally, the FACT-G group mean scores at baseline (apalutamide plus ADT 79.50; placebo plus ADT 78.81) were similar to the FACT-G population norm for adult men (80.9, SD 17.4). CS Figures 34 and 35 show that there were no statistically significant differences between the trial arms in FACT-P total scores or in FACT-G scores and patients maintained their overall HRQoL in both treatment arms.

3.2.6.6 Subgroup analyses

The company's decision problem includes a subgroup described as 'patients ineligible or unsuitable for chemotherapy' but no evidence is provided for this subgroup directly from the TITAN trial. It is not clear from the CS what proportion of TITAN patients were ineligible or unsuitable for chemotherapy but the ERG notes that 10.7% of TITAN trial participants had received prior docetaxel chemotherapy and 9.1% received docetaxel as a subsequent therapy. It is unclear what proportion of the remaining patients would be assessed as ineligible or unsuitable to receive docetaxel. The CS does not present results separately for those participants in the TITAN trial who were eligible for chemotherapy.

In CS section B.2.13 the company presents the results of analyses conducted across a range of pre-defined subgroups for the co-primary outcomes of rPFS (CS Figure 37) and OS (CS Figure 36). For both outcomes, the results for the majority of the subgroups were consistent with those of the overall TITAN trial population. Exceptions for the subgroup analyses of OS were for the subgroups by patients with prior docetaxel use (HR 1.27) and visceral disease at baseline (HR 0.99) where subgroups were small and with unbalanced sample sizes. The company formally tested interaction effects and found no statistically significant differences in the treatment effect for prior docetaxel or for visceral disease at baseline.

3.2.6.7 Safety outcomes

The company's safety analysis includes all patients randomised who received at least one dose of study treatment, 524 patients in the apalutamide plus ADT arm and 527 patients in the placebo arm.

3.2.6.7.1 Treatment duration, dose interruptions and dose modifications

At the time of clinical cut-off (23rd November 2018) treatment exposure was slightly longer in the apalutamide plus ADT arm of the TITAN trial (median of 20.5 months versus placebo plus ADT median of 18.3 months) but a greater proportion of patients in the apalutamide plus ADT arm were still receiving treatment (66% versus 46% in the placebo plus ADT arm).

The CS summarises the dose reductions and interruptions in CS Table 45. The proportion of patients requiring dose reductions was low (7.3% in the apalutamide plus ADT arm and 2.1% in the placebo plus ADT arm) whereas dose interruptions occurred in a greater proportion of patients ([redacted] in the apalutamide plus ADT arm and [redacted] in the placebo plus ADT arm).

3.2.6.7.2 Summary of adverse events

The company's summary table of adverse events is reproduced below in Table 17.

Table 23 Summary of adverse events TITAN trial (Safety population)

	Apalutamide plus ADT (n = 524)	Placebo plus ADT (n = 527)
TEAEs, total, n (%)	507 (96.8)	509 (96.6)
TEAEs, drug-related, n (%)	315 (60.1)	219 (41.6)
TEAEs, Grade 3-4, n (%)	221 (42.2)	215 (40.8)
TEAEs, Grade 3-4, drug-related, n (%)	66 (12.6)	31 (5.9)
SAEs, total, n (%)	104 (19.8)	107 (20.3)
SAEs, drug-related, n (%)	10 (1.9)	4 (0.8)
SAEs, Grade 3-4, n (%)	84 (16.0)	86 (16.3)
TEAE-related discontinuation, n (%)	42 (8.0)	28 (5.3)
TEAE-related discontinuation, drug-related, n (%)	17 (3.2)	4 (0.8)
TEAE-related deaths, n (%)	10 (1.9)	16 (3.0)
TEAE-related deaths, drug-related, n (%)	0 (0.0)	0 (0.0)
Deaths within 30 days of last dose, n (%)	18 (3.4)	23 (4.4)
Death due to prostate cancer, n (%)	8 (1.5)	7 (1.3)
Death due to AE, n (%)	10 (1.9)	16 (3.0)

Source: reproduction of CS Table 46, footnotes edited by the ERG
AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event
Notes: Aes and concomitant therapies were assessed continually from informed consent until 30 days after the last dose of study drug.

3.2.6.7.3 Summary of treatment emergent adverse events

The company state that the most commonly recorded adverse events in the TITAN trial were expected *a priori* and were consistent with the safety profile that had already been observed in the SPARTAN trial for nmHRPC patients. The company highlight skin rash which occurred in a higher proportion of TITAN trial participants in the apalutamide plus ADT arm (27.1%) in comparison to the placebo plus ADT arm (8.5%) and is considered as an AESI (see section 3.2.6.7.5 of this report).

The ERG has tabulated the most frequently reported TEAEs in the TITAN trial from the CS (Table 24) with events ordered by the proportion in the apalutamide plus ADT arm experiencing that event).

Table 24 Most frequently reported TEAEs in the TITAN trial (preferred terms reported in ≥15% of patients)

AE, n (%)	Apalutamide plus ADT N=524	Placebo plus ADT N=527
Rash (grouped term[a])	27.1%	8.5%
Hot flush	22.7%	16.3%
Hypertension	17.7%	15.6%
Back pain	17.4%	19.4%
Arthralgia	17.4%	14.8%
Weight increased	10.3%	16.9%

Source: Text in CS Section B.2.16.3
[a] A grouped term was used to combine related preferred terms to more accurately assess the incidence and characteristics of rash.

Grade 3 and 4 adverse events

The company summarise treatment-emergent grade 3 and grade 4 Aes (reported in 5% or more of patients) in CS Table 47. The results were similar for both trial arms indicating that the addition of apalutamide to ADT was not associated with an additional incidence of grade 3 and grade 4 TEAEs (42.2% in the apalutamide plus ADT arm and 40.8% in the placebo plus ADT arm) Overall only 4% of patients experienced Grade 4 events.

3.2.6.7.4 Summary of serious adverse events

The CS does not tabulate data for commonly reported SAEs (occurring in ≥ 1% of patients in either arm) but does list two events that occurred at a higher incidence in the apalutamide plus ADT arm than the placebo plus ADT arm [redacted] There were three SAEs that were only reported among patients in the apalutamide plus ADT arm [redacted].

3.2.6.7.5 Summary of adverse events of special interest

The pre-defined AESI were skin rash, fall, fracture, hypothyroidism and seizure (these were identical to the AESIs defined for the SPARTAN trial, except that ischaemic heart disease

was not included. The SPARTAN trial CSR[17] indicates that [redacted]). The incidence of AESI was higher in the apalutamide plus ADT arm for skin rash and hypothyroidism than in the placebo plus ADT arm but the rates of fall, fracture and seizure were similar in the two trial arms (CS Table 48).

The CS provides further detail on skin rash. The onset of skin rash typically occurred within the first three months of apalutamide treatment and a grade 3 skin rash was reported in [redacted] of apalutamide + ADT patients in comparison to [redacted] of placebo plus ADT patients. [redacted] When skin rash occurred, it was actively managed with steroid or antihistamines and the rate of discontinuation due to skin rash was low in both treatment arms (1.5% in the apalutamide plus ADT arm and 0.2% in the placebo plus ADT arm). Further details on the characteristics of skin rash are presented in CS Table 49.

3.2.6.7.6 Summary adverse events leading to death

Deaths that had occurred within 30 days of the last dose of study drug by the clinical cut-off (23rd November 2018) are summarised below in Table 25. The company states that no deaths in either treatment arm were related to treatment.

Table 25 Summary of adverse events leading to death in TITAN

	Apalutamide plus ADT (N=524)	**Placebo plus ADT (N=527)**
Deaths within 30 days of the last dose of study drug, %	3.4	4.4
Deaths due to an adverse event, n (%)	10 (1.9)	16 (3.0)
Deaths due to Aes occurring in follow-up, n	0	4
Source: text in CS B.2.16.2		

3.3 Critique of studies included in the indirect treatment comparison (ITC)

3.3.1 Rationale for ITC

As ADT was the only relevant comparator in the decision problem for the nmHRPC patient group the company did not consider an ITC to be necessary as apalutamide plus ADT was directly compared with ADT (plus placebo) in the SPARTAN trial. The ERG concurs with this decision. However, for the mHSPC patient group the TITAN trial did not include a comparison between apalutamide plus ADT and docetaxel plus ADT. Hence, the company conducted an ITC to assess the relative effectiveness and safety of these two treatments, for six outcome measures:

- OS
- rPFS
- PFS
- Time to PSA progression
- Overall AEs
- SAEs

In the following sub-sections describe and critique the ITC focusing on the two outcome measures that directly inform the cost-effectiveness analysis: OS and PFS.

3.3.2 Identification, selection and feasibility assessment of studies for ITC

The company's SLR identified 38 RCTs which met their predefined inclusion criteria (CS appendix D.1). These 38 RCTs were then assessed for their feasibility for inclusion in network meta-analysis (NMA). Studies were assessed on: availability of an appropriate comparator arm (i.e. ADT); reporting of comparable outcomes of interest; and sufficiently homogenous study characteristics. The feasibility assessment identified four such RCTs for inclusion in the NMA: the pivotal phase III TITAN trial, plus three RCTs linking docetaxel plus ADT to apalutamide plus ADT through the common comparator of placebo plus ADT: CHAARTED, GETUG, & STAMPEDE (Figure 13). The ERG notes that the company did not provide the reason(s) for exclusion of each of the remaining 34 trials, thus we cannot fully assess the reliability of the company's selection of included/excluded studies.

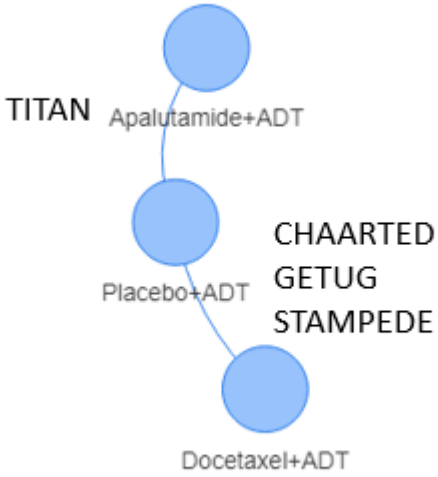


Figure 13 Network of evidence for indirect comparison of apalutamide plus ADT versus docetaxel plus ADT

NB. Diagram drawn by the ERG

The ERG asked the company to clarify whether the LATITUDE trial[15] (which compared abiraterone plus ADT plus prednisone versus placebo plus ADT) and the abiraterone plus ADT arm from the STAMPEDE trial could have been included in the NMA, as this would have provided additional indirect evidence for apalutamide plus ADT versus docetaxel plus ADT and for docetaxel plus ADT versus placebo plus ADT. We noted that these trial arms had been included in a published NMA of abiraterone acetate plus prednisone versus docetaxel in mHSPC sponsored by the company (Feyeraband et al, 2018[30]). The company clarified that LATITUDE[15] and the Feyeraband et al[30] NMA focused on narrower patient population than the decision problem: newly diagnosed patients with high-risk and/or high volume mHSPC. They also clarified that the abiraterone plus ADT arm of STAMPEDE was only included in a sensitivity analysis in the Feyeraband et al[30] NMA as data were not available for high-risk and/or high volume mHSPC patients. They also state that the abiraterone plus ADT arm does not add any additional evidence on relevant comparators when LATITUDE[15] is excluded. The ERG therefore agrees with the company's justification not to include these studies in the current NMA.

3.3.3 Clinical heterogeneity assessment

Table 37 compares study and patient characteristics, respectively, across the four included studies. The ERG observes some differences between the studies (clinical heterogeneity) in terms of the following characteristics at baseline:

- ECOG / WHO performance status score (0; ≥ 1) (GETUG higher proportion of PS 0)

- Proportion of patients with newly diagnosed mHSPC (STAMPEDE 100%)
- Proportion of patients with high volume disease (STAMPEDE lower)
- Proportion of patients with a Gleason score of 8 to 10 (indicating high-grade prostate cancer) (GETUG lower)
- Median PSA levels

In addition, the company reported an I^2 value of 67.4% from a pairwise meta-analysis of the docetaxel plus ADT vs placebo plus ADT trials, indicating moderate to substantial statistical heterogeneity. The company did not state which, if any, of the characteristics in CS Table 37 are confirmed or potential treatment effect modifiers.

The ERG requested the company to present evidence for or against treatment effect modifiers (clarification question response A12). The company examined the subgroup analyses within the four trials and reported that the following factors showed evidence as treatment effect modifiers in at least one study:

- Baseline PSA level
- Volume of disease
- Newly diagnosed patients versus patients progressed to metastatic from localised disease
- Lactic acid dehydrogenase (LDH)
- ECOG performance status score (0 versus 1)
- Number of bone lesions at baseline (<=10 vs >10)
- Presence of visceral disease

That the other three trials did not examine these factors for possible effect modification does not provide proof that they are not. The company examined the between-trial differences for each of these factors and concluded the net effect of these imbalances on the ITC was likely to be minimal. However, most of the evidence for or against treatment effect modifiers comes from TITAN subgroup analyses (Table 6, clarification question responses).
The ERG notes that the imbalances between trials in ECOG performance status, proportion of newly diagnosed disease, and Gleason Score 8-10 are likely to favour docetaxel plus ADT but the impact of PSA level is unclear.

3.3.4 Similarity of treatment effects

The NMA assumed similarity of the four ADT arms, and of the three docetaxel plus ADT arms. This was confirmed by the ERG's clinical experts. The TITAN trial has a relatively

short follow-up at time of this appraisal, thus the company's base case analysis included interim data cuts closest in follow up to TITAN's (22.7 months for TITAN, 28.9 months for CHAARTED, 43 months for STAMPEDE, and 50 months for GETUG (CS Table D.50)). A sensitivity analysis for OS included the longest data cuts available (CS Table D.51). These sensitivity analysis results were consistent with the base case (CS Table D.54). A further data cut from TITAN is expected as part of technical engagement (company decision problem form, section 1).

The definition of outcome measures appears to be comparable across the studies. For brevity we have focused our critique on OS and PFS as these directly inform the economic model.

3.3.5 Risk of bias assessment for studies included in the ITC

The company did a risk of bias / study quality assessment of the four trials (CS Appendix D3). They conclude that there was an overall low risk of bias for all studies except the CHAARTED trial, which was judged at high risk of bias due to its open-label nature, and the STAMPEDE trial which was judged to be medium risk. Only a summary of risk of bias judgements by bias domain is given, without any further detail on the rationale for the judgement, making it difficult for the ERG to verify their judgements. The ERG notes that the comparator trials have been included in previous NICE prostate cancer TAs, and there does not appear to be a sufficient rationale for excluding any of these from the ITC (e.g. in a sensitivity analysis) on the basis of risk of bias.

ERG conclusion

The ERG notes the ITC was informed by a comprehensive SLR, which is likely to have identified all relevant trials for inclusion. The four included trials are generally of good quality, and low risk of bias (with some exceptions), and they provide a sufficient evidence base for indirect comparison. There is uncertainty about which patient and study characteristics are effect modifiers for apalutamide. There is evidence of heterogeneity between the trials in terms of certain baseline patient characteristics, some of which are potential effect modifiers. The is a limitation of the NMA which should be taken into account in the interpretation of its results.

3.4 Critique of the indirect treatment comparison statistical methods

3.4.1 Data inputs to the NMA

The ERG found that the reporting of some of the data inputs to the NMA were unclear in the CS. In response to a clarification question (A15) the company provided the data used in the OS and PFS base case and sensitivity analyses (clarification question responses Table 18 & 19). Data cuts from the trials most similar to TITAN were used in the base case, as noted in section 3.3.4 above.

The company obtained individual patient data (IPD) for the STAMPEDE trial to calculate treatment effects on PFS, TTPSA, AEs, and SAEs since published data for this trial were only available for OS (clarification question response A10). The company also clarified that analysis of the IPD data was aggregated prior to inclusion in the NMA (clarification question response A10).

The ERG notes that some patients in the docetaxel comparator trials in the NMA received life-prolonging treatments later in the course of their disease, including chemotherapy and novel prostate cancer therapies. Some patients will have received more than one novel therapy during their disease, which, as discussed earlier, would not be permitted in the NHS. Survival estimates from these trials will be affected potentially confounded by the subsequent treatments, and to our knowledge these have not been adjusted for treatment switching/crossover by the trial authors. The company would not be able to adjust the survival estimates in the economic model unless they had access to IPD. Few patients in the TITAN trial had received subsequent treatments at the interim analysis, thus potential confounding is less of a problem as regards the apalutamide data.

3.4.2 Statistical methods for the NMA

The company used a Bayesian approach to NMA, using WinBUGS software. The ERG has checked the programming code (as requested from the company; clarification question response A15) and were able to replicate the company's results for OS and PFS using the data reported in Table 18 of the company's clarification question response document.

3.4.2.1 Assessment of proportional hazards

The NMA assumes that the proportional hazards assumption is applicable to the included survival data. This assumption was tested using standard available methods: the Schoenfeld test, Schoenfeld residual plots, and log cumulative hazards plots (CS section D).

The CS reports that proportional hazards assumption did not hold for the CHAARTED trial for the outcome of OS, and the GETUG trial for the outcome of PFS. The proportional hazards tests in CS Appendix D only included OS, hence the ERG requested the company report them for other time-to-event endpoints (clarification response A14). The ERG also requested the company conduct scenario analyses excluding studies where proportional hazards did not hold, or to consider using an NMA based on the assumption of time varying hazards, such use of fractional polynomials. In response, the company clarified that the proportional hazards assumption held for the NMA base case for the outcome of OS, and that it was a later data cut of CHAARTED in which proportional hazards were violated. The company conducted the requested scenario analyses on their sensitivity analysis, the results of which differed little from the NMA base case results (clarification question response tables 16 & 17).

The company also highlighted that the breach of proportional hazards in the CHAARTED trial occurred at the end of the dataset, where overlapping survival curves represents would a conservative analysis. The company therefore chose not to conduct a time-varying hazard based NMA model stating that there would be insufficient data to do this robustly and that their scenario analysis effectively demonstrated the impact on results. The ERG agrees this is reasonable. However, in the base case OS, there is also a possibility that proportional hazards may not hold for the GETUG-AFU 15 trial despite the non-significant Schoenfeld global test (p=0.143) (CS Appendix D, Figure 7). The Schoenfeld residuals plot indicates proportional hazards may be violated in the tail end of the data (around 36 months onwards). As the OS curves are diverging, this may bias analysis against docetaxel.

3.4.2.2 Choice between random effects and fixed-effect models

Only fixed effect NMA results were presented in the CS, based on the justification that fixed effect is more appropriate than random effects in the presence of a small evidence base, as is the case here (i.e. only four trials). Since there is potential clinical heterogeneity across the included trials, the ERG asked the company to present random effects results, and also to clarify whether they had considered use of an informative prior (clarification question A13). Random effects are also supported by the company's calculated I^2 statistic for the pairwise meta-analysis of the three docetaxel plus ADT trials.

In response, the company presented a range of random effects models using different priors on the random effect standard deviation (clarification response document Tables 8, 10, 12 &

14). The company also noted that the small networks mean uncertainty will be overestimated with random effects (The between studies variance was not reported, nevertheless the ERG agrees.) In response, the company used two informative priors on the random effects standard deviation: Uniform(0,1), a “somewhat” informative prior, and Uniform(0,0.4) a “more” informative prior for scenario analyses. The typical uninformative (“vague”) prior for random effects Uniform(0,5) used in the TSD documentation was not used in the company analyses as this led to implausible heterogeneity due to the low number of studies. The median HRs for the random effects models with the informative priors were very similar to the fixed effects albeit the 95% credible intervals were wider. The ERG welcomes the presentation of these analyses; given the presence of clinical heterogeneity fixed effect models are likely to underestimate uncertainty, hence the informative priors represent useful scenarios. That said, the ERG conducted a further scenario analysis for OS and PFS using an alternative informative prior; the half-normal prior referred to in NICE DSU TSD3. The results approximated the Uniform(0,1) prior used in the CS (section 3.6 below).

3.4.3 Summary of ERG critique of the NMA

- The methodology used by the company to conduct the NMA is appropriate to the clinical trial data available. The methodology has been described and applied correctly.
- Whilst the company has addressed violation of proportional hazards through sensitivity analyses, there is further evidence of a potential violation in proportional hazards in OS for the GETUG trial, which suggests a time-varying hazard based NMA could have been contemplated. The effect on the analysis is unclear but may bias against docetaxel plus ADT.
- The fixed effect models presented in the company base case will underestimate uncertainty due to heterogeneity. A random effects model is more appropriate but has limited ability to estimate between study variation due to the low number of studies in the network.
- The use of an informative prior for the random effects standard deviation offers a compromise. The company and the ERG have both conducted random effects models using different informative priors with similar results

3.5 Results of the indirect comparison

The fixed-effect NMA results for efficacy and safety are presented in Table 22 and Table 23, respectively. [redacted]

Table 26 Company base case NMA efficacy results (fixed effects)

Comparison		OS	rPFS	rPFS + PFS / FFS	TTPSA
Apalutamide plus ADT vs ADT alone	HR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]
	Probability that HR is less than 1	[redacted]	[redacted]	[redacted]	[redacted]
Apalutamide plus ADT vs docetaxel plus ADT	HR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]
	Probability that HR is less than 1	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; CrI, credible interval; HR, hazard ratio; NMA, network meta-analyses; OS, overall survival; rPFS, radiographic progression-free survival; SRE, skeletal related; TPSA, time to PSA progression.
Source: CS Table 40

None of the safety results were statistically significant apart from a reduction in SAEs which favoured apalutamide plus ADT versus docetaxel plus ADT.

Table 27 Company base case NMA safety outcomes (fixed effects)

Comparison		Overall AEs	SAE
Apalutamide plus ADT vs ADT alone	Median OR (95% CrI)	[redacted]	[redacted]
	Probability that OR is less than 1	[redacted]	[redacted]
Apalutamide plus ADT vs Docetaxel plus ADT	OR (95% CrI)	[redacted]	[redacted]
	Probability that OR is less than 1	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; AE, adverse events; CrI, credible intervals; NMA, network meta-analyses; SAE, serious adverse events.
Source: CS Table 42

The company's random effects model results using the informative U(0,1) prior from the response to clarification question A13 are shown in

Table 28.

Table 28 Company NMA efficacy results (random effects)

Comparison		OS	rPFS	rPFS + PFS	TTPSA
Apalutamide plus ADT vs ADT alone	HR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]
	Probability that HR is less than 1	[redacted]	[redacted]	[redacted]	[redacted]
Apalutamide plus ADT vs docetaxel plus ADT	HR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]
	Probability that HR is less than 1	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; CrI, credible interval; HR, hazard ratio; NMA, network meta-analyses; OS, overall survival; RE, random effects; rPFS, radiographic progression-free survival; TPSA, time to PSA progression.
Source: Clarification responses Table 8

3.6 Additional work on clinical effectiveness undertaken by the ERG

The ERG conducted an additional random effects analysis for OS and PFS. Rather than use the Uniform informative priors used by the CS, the ERG adopted the half-normal informative prior Half-Normal(0,32^2) used in NICE TSD3. As stated above, these results were similar to the company results using the Uniform(0,1) "somewhat" informative prior (Table 29). The ERG believes the random effects model more accurately represents uncertainty around the mean estimates.

Table 29 ERG NMA OS and PFS results (random effects using half-normal prior)

Comparison		OS	rPFS
Apalutamide plus ADT vs ADT alone	HR (95% CrI)	[redacted]	[redacted]
Apalutamide plus ADT vs docetaxel plus ADT	HR (95% CrI)	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; CrI, credible interval; HR, hazard ratio; NMA, network meta-analyses; OS, overall survival; rPFS, radiographic progression-free survival; SRE, skeletal related; TPSA, time to PSA progression.

4 COST EFFECTIVENESS

4.1 Critique of the cost-effectiveness review

4.1.1 nmHRPC

The company conducted a SLR to identify cost-effectiveness studies for patients with nmHRPC. The original search was performed between July and August 2018 and was followed by two search updates, the first one between November and December 2018 and the second one between April and June 2020 (CS Appendix G.2).

The company performed their searches in relevant electronic databases, conference websites and HTA databases (CS Appendix Table G.1). The inclusion and exclusion criteria are presented in CS Appendix Table G.2. The ERG notes that, according to the inclusion criteria, studies for patients with nmHRPC, rather than high-risk nmHRPC, were included to retain potentially relevant data.

Seven relevant cost-effectiveness studies were identified by the SLR (CS Appendix Figure 25). Of these studies, one is the NICE technology appraisal for enzalutamide (NICE TA580), and four assess apalutamide from international healthcare perspectives. CS Appendix Tables G.32, G.33 and G.34 report the main characteristics of each included study and CS Appendix Table G.36 presents the company's quality assessment. The references of excluded studies with reasons for exclusion are reported in CS Appendix Table G.35. Table 30 presents the characteristics of the four included studies assessing apalutamide.

Table 30 Characteristics of studies assessing apalutamide identified through the systematic literature review for nmHRPC

Study name	Type of study	Population	Perspective/ Time horizon	Type of model	Intervention/ Comparator	Model health states	ICER per QALY
ICER (Draft Evidence Report, July 12, 2018)	Cost–utility	Patients with nmHRPC who were at high risk for the development of metastases, which was defined as a PSA doubling time of 10 months or less during continuous ADT	US health care and societal/ Lifetime	Combination of partitioned survival approach and Markov approach	APA plus ADT, ENZA plus ADT, ADT alone	MFS, asymptomatic progression, symptomatic progression, death	APA plus ADT vs. ADT alone: US$68,000
CADTH 2018 (Manufacturer's submission)	Cost–utility		Canadian health system/ 15 years (Manufacturer's submission), 10 years (EGP reanalysis)	Partitioned survival approach	APA plus ADT, ADT alone	MFS, mHRPC, death	CAN$151,811 (Manufacturer's submission), CAN$198,826 (EGP reanalysis)
Zhou 2018	Cost effectiveness analysis	Patients with nmHRPC	US societal/ Lifetime	Markov model	APA versus placebo as first-line therapy in nmHRPC, AAP plus prednisone, ENZA, DOX and Sipuleucel-T as second-line therapy	Stable disease, progressed disease, death	US$680,089
Tsiatas 2019	Cost-utility	Patients with nmCRPC	Greek health care/ NR	Partitioned survival model	APA plus ADT, ENZA plus ADT	nmHRPC, mHRPC, death	€6,998-€34,814

Source: reproduced from CS Appendix Tables G.32, G.33 and G.34.
AAP: abiraterone, ADT: androgen deprivation therapy, APA: apalutamide, DOX: docetaxel, EGP: Economic Guidance Panel, ENZA: enzalutamide, MFS: metastasis-free survival, mHRPC: metastatic hormone resistant prostate cancer, nmHRPC: non-metastatic hormone resistant prostate cancer, nmCRPC: non-metastatic castration resistant prostate cancer, NR: not reported, PSA: prostate specific antigen, US: United States of America.

4.1.2 mHSPC

The company conducted a SLR to identify cost-effectiveness studies for patients with mHSPC published since 2005. The original search was conducted in September 2015 and was followed by five search updates: July 2017, May 2019, June 2019, November 2019 and May 2020 (CS Appendix G.6.1).

The company performed their searches in relevant electronic databases and conference websites (CS Appendix Table G.37, CS Appendix G.6.2). No HTA databases were searched. The inclusion and exclusion criteria are presented in CS Appendix Table G.56.

Forty-four relevant studies from 49 publications were identified through the SLR: 30 are cost-effectiveness studies and 14 are studies focused on costs and healthcare resource use (CS Appendix Figure 26). Of the cost-effectiveness studies, four are conducted from a UK perspective but do not include apalutamide. One cost-effectiveness study evaluates apalutamide from a Canadian perspective. CS Appendix Tables G.57, G.58, G.59, G.60 and G.61 report the main characteristics of each cost-effectiveness study and CS Appendix Table G.63 presents an assessment of their quality. CS Appendix section I.2 Table I.1 summarises the cost and healthcare resource use studies. Excluded studies with reasons for exclusion are reported in CS Appendix Table G.62. Table 31 presents the characteristics of the included study assessing apalutamide.

Table 31 Characteristics of the study assessing apalutamide identified through the systematic literature review for mHSPC

Study name	Type of study	Population	Perspective/ Time horizon	Type of model	Intervention/ Comparator	Model health states	ICER per QALY
Parmar et al.	Cost-utility analysis	Patients with mCSPC	Canadian healthcare/ Lifetime	State-transition model with probabilistic analysis	APA plus ADT, ADT alone	NR	CAN$ 160,483

Source: reproduced from CS Appendix Tables G.57, G.58, G.59, G.60 and G.61.
ADT: androgen deprivation therapy, APA: apalutamide, mCSPC: metastatic castration sensitive prostate cancer, NR: not reported.

ERG conclusion

The ERG considers the company's review of cost-effectiveness evidence comprehensive and appropriate. The sources searched (including all recommended databases) is adequate, the search structure and syntax are accurate, the search

strategies reflect the disease population, the volume of searches is large but consistent, the searches are reasonably up to date and the reporting is clear.

4.2 Critique of the submitted economic evaluation

4.2.1 NICE reference case checklist

Table 32 shows the requirements of the NICE reference case and the ERG's judgment on whether that the company's economic analysis adequately meets the reference case.

Table 32 NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes, lifetime horizon (32 years)
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes, EQ-5D used in economic model.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes

Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

4.2.2 Model structure

4.2.2.1 Overview of the model structure

The model structure was based on three factors: the disease pathway, the availability of data to inform the analysis and feedback from the NICE appraisal committee on previous NICE submissions for prostate cancer.

The prostate cancer disease pathway is described earlier in this report (see section 2.2.3). Patients with high-risk nmHRPC and mHSPC progress over time and develop mHRPC, at which time they may receive a number of subsequent therapies until death. The company assumes that progression to mHRPC is driven by MFS for patients with nmHRPC and by rPFS for patients with mHSPC. The definition of each of these measures is described in in CS Table 51.

Efficacy data to inform the comparison between apalutamide plus ADT and ADT alone for nmHRPC are from the SPARTAN trial which has MFS as its primary endpoint. The TITAN trial informs the same comparison for mHSPC, with rPFS and OS as co-primary endpoints. The comparison of apalutamide plus ADT versus docetaxel plus ADT for the mHSPC indication is based on the NMA as described in section 3.3.

CS Tables 52 and 53 summarise the model structures and main features of the economic analysis for prostate cancer previously submitted to NICE and feedback from the NICE appraisal committees and/or ERGs on those submissions. In general, partitioned survival models have been accepted and considered appropriate, although models including multiple health states for post-progression survival have raised some concerns mainly around the ability of this approach to truly represent UK clinical practice.

In addition to the three factors described above, the selection of the model structure for the current appraisal was also based on the guidance reported in NICE TSD 19,[31] which recommends using a partitioned survival analysis alongside state transition modelling. The company also argues that with a partitioned survival analysis it is possible to apply more than one key outcome, more than one trial data cut and also HR to the independent curves.

Therefore, considering all these factors, the company constructed a partitioned survival analysis model with multiple health states to model post-progression transitions. This approach was validated by experts advising the company. The model has weekly cycles and a lifetime horizon (32 years). The structure is described in CS B.3.2.2 and illustrated in CS Figure 40, reproduced in Figure 14 below.

The model consists of three main health states: progression-free survival (PFS), progressive disease and death. Patients with nmHRPC or mHSPC start in the PFS health state, in which they receive treatment with either apalutamide plus ADT or the comparator intervention(s) (ADT alone for nmHRPC; ADT alone or docetaxel plus ADT for mHSPC). In each cycle, patients can remain progression-free or they can progress to mHRPC according to the MFS/rPFS rates, respectively. In the PFS health state, patients receiving apalutamide can be on-treatment or off-treatment, according to the time to treatment discontinuation (TTD) data. Once patients progress, they will receive up to three lines of subsequent therapy. PFS2 curves inform the transition between the first and second and third line mHRPC health states. Survival curves are used to model PFS, PFS2 and OS.

The proportion of patients in each health state is informed by the area under the curve approach, where the area between MFS/rPFS and PFS2 is calculated to estimate the time spent in the first line mHRPC health state and the area between PFS2 and OS to estimate the time spent in the second and third line mHRPC health states. Due to the absence of data from the SPARTAN and TITAN trials, mean health state durations are based on those used in NICE TA387 for abiraterone for treating mHRPC before chemotherapy is indicated.

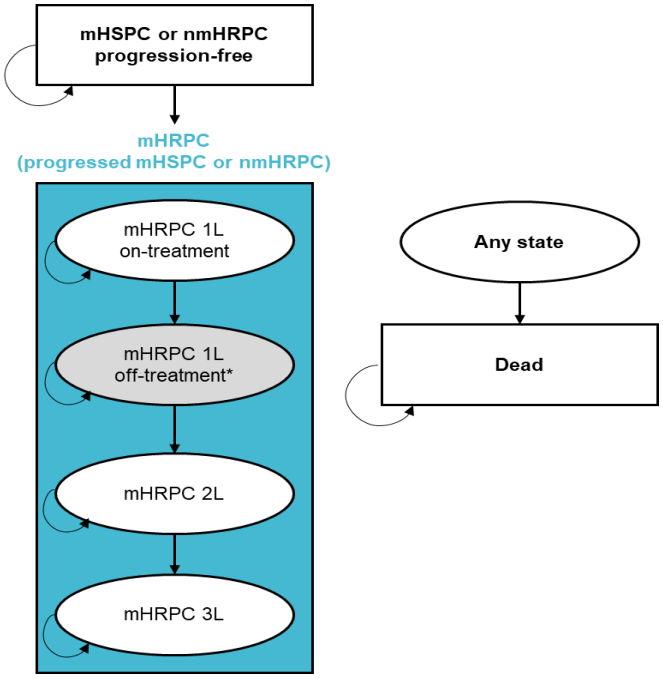


Figure 14 Economic model diagram

Source: reproduced from CS Figure 40.
1L: first-line; 2L: second-line; 3L: third-line; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; nmHRPC: non-metastatic hormone-relapsed prostate cancer.
*mHRPC 1L off-treatment is only included in the scenario analysis of the model.

The progression rates (PFS and PFS2) and death rates (OS) are discussed in more detail later in this report (section 4.2.6).

4.2.2.2 ERG critique of model assumptions

The CS includes a table of modelling assumptions (CS Table 84). The ERG's views of these assumptions are presented in Table 33.

Table 33 Company model assumptions

Assumption	Justification	ERG comments
Generalisability		
Patient characteristics, efficacy and safety were derived from the TITAN and SPARTAN trials and were assumed to be representative of the mHSPC and nmHRPC populations in the UK.	• Clinical feedback confirmed that the patients in the TITAN and SPARTAN trials were reasonably reflective of patients in UK clinical practice. The potential impact of the one novel therapy restriction in UK clinical practice has also been accounted for in the survival analysis.	• We agree
Model structure		

The partitioned survival model is a suitable model structure.	• This is based on the guidance set out in NICE DSU TSD 19, the data available for this submission and committee feedback from previous submissions.	• We agree
Radiographic progression-free survival and metastases-free survival are suitable proxies for disease progression in mHSPC and nmHRPC, respectively.	• This was firstly based on the findings from the clinical advisory boards and precedent from previous prostate cancer submissions (as summarised in CS Table 53).	• We agree
Docetaxel is given for a maximum of six cycles.	• This is applied according to NHS England commissioning policy. This is also in line with the dosing schedules used in the CHAARTED and STAMPEDE studies and reflects UK clinical practice. In GETUG-AFU 15, patients received up to 10 cycles of therapy. Therefore, the model overestimates docetaxel effectiveness relative to the cost, and thus assuming six cycles of therapy is a conservative assumption.	• We agree
Survival projections		
It was assumed that: • TTD cannot be longer than PFS • PFS cannot be longer than PFS2 • PFS2 cannot be longer than OS • OS cannot be longer than survival in the general population	• TTD: In clinical practice, apalutamide is a therapy where patients are treated until progression • PFS: Patients need to progress on treatment before starting a first-line treatment for mHRPC. Therefore, MFS/rPFS is always shorter than PFS2 • PFS2: Patients cannot be treated after death • OS: It is unlikely that patients with mHSPC or nmHRPC live longer than the general population with the same age	• We agree
Utilities		
Baseline utility in nmHRPC and mHSPC was assumed to be similar for patients receiving apalutamide plus ADT and ADT alone.	• Baseline utility before start of treatment was similar in the apalutamide plus ADT arm compared with the placebo plus ADT arm in the SPARTAN and TITAN trials.	• We agree
Patients receiving docetaxel in mHSPC are assumed to experience a utility decrement of -0.02 while they are receiving treatment (18 weeks).	• This value was taken from a time trade-off study utility study and is consistent with the utility decrement of -0.02 estimated from the STAMPEDE trial was applied for one year in a cost-	• We agree

	effectiveness model presented in the Woods et al. (2018) publication.[32]	
Subsequent treatments		
Post-progression survival data are reflective of outcomes in UK clinical practice.	• The novel therapy analysis that adjusted survival outcomes for the one novel therapy restriction in UK clinical practice demonstrated that this restriction has only a small impact on the survival data.	• There is uncertainty because the adjustments for treatment switching conducted by the company could not be verified by the ERG because the IPD from the pivotal trials were not provided
Most patients will receive three or fewer lines of active treatment for mHRPC.	• This assumption was validated during the clinical advisory board, with clinicians stating that patients would typically receive up to two active therapies, followed by BSC, but some could receive a third.	• We agree
ADT is received until death.	• This is reflective of UK practice, as advised by UK clinicians. It is also supported by TA404 (degarelix for treating advanced hormone-dependent prostate cancer).[33] This is a conservative assumption as patients in the apalutamide arm have longer OS compared with those treated with ADT alone or docetaxel. Therefore, this assumption increases treatment costs for patients treated with apalutamide relative to patients on docetaxel or ADT alone.	• We agree
Source: reproduced from CS Table 84. 1L: first line; 2L+: second and later lines; ADT: androgen deprivation therapy; AE: adverse event; BSC: best supportive care; HRQL: health-related quality of life; mHRPC: metastatic hormone-relapsed prostate cancer; MFS: metastases-free survival; mHSPC: metastatic hormone-sensitive prostate cancer; nmHRPC: non-metastatic hormone-relapsed prostate cancer; OS: overall survival; PartSA: partitioned survival analysis; PFS: progression-free survival; PFS2: secondary progression-free survival; TTD: time to treatment discontinuation.		

Treatment waning assumption

The company states that the OS data from both SPARTAN and TITAN demonstrate a statistically significant treatment effect with no evidence that the OS curves converge over time. Therefore, no additional treatment waning was applied to the OS curves in the company's base case. Given the absence of data to allow for the assessment of the long-

term treatment effect of apalutamide, the company conducted a scenario to assess the impact of treatment waning on OS over time (see section 5.2**Error! Reference source not found.** below). In this scenario, the waning effect reduces the treatment effect from 100% to 0% over a 5-year period starting from year 10.

According to NICE guidance, the duration of treatment effect is an important model assumption, therefore an analysis of the intervention's hazards from clinical trials coupled with clinical expert opinion and biological plausibility should be considered in order to assess the validity of extrapolated data. In addition, some scenarios changing these assumptions are also recommended.

The ERG plotted the hazard curves for each intervention from the KM data of the relevant clinical trials (SPARTAN for nmHRPC and TITAN for mHSPC), however it was inconclusive whether there is a tendency for declining treatment benefit or not. The clinical experts advising the ERG do not expect to see a treatment waning effect with apalutamide since no waning effect was observed with abiraterone in a longer follow-up setting, in particular, in the STAMPEDE trial [34]

As reported by Antonarakis[35], in the first-line castration-resistant prostate cancer (CRPC) setting, resistance to abiraterone or enzalutamide typically develops after 9 to 15 months of treatment with either agent. Given that there is some similarity in the mechanisms of action between apalutamide and enzalutamide, [36] [37] it would not be unreasonable to assume that waning effect and its time frame are likely to be similar (or at least not very different) for these treatments. Our expert considers this assumption reasonable. However, this study was conducted in a more advanced phase of the disease, therefore it is unclear how generalizable these results are for the earlier states of the disease, namely nmHRPC and mHSPC. In addition, resistance to abiraterone or enzalutamide does not necessarily imply that there would be a treatment waning effect.

Based on the above, we do not have sufficient evidence to conclude on the best approach regarding the duration of treatment benefits. Therefore, we agree with the company's assumption of not including treatment waning in the base case but inclue it as a scenario analysis (as recommended by NICE guidance). The ERG also added a scenario analysis changing the treatment waning period from 5 to 10 years since this has not been explored in the CS (see section 6.1).

ERG conclusions

A partitioned survival analysis model is a common approach in economic evaluation for oncology and has been applied in previous NICE appraisals for prostate cancer. The company used multiple health states to model post-progression survival. The ERG considers that the chosen approach is appropriate, is consistent with NICE guidance and reflects UK clinical practice. The ERG explores different treatment waning periods as scenario analyses.

4.2.3 Population

The patient population included in the economic evaluation is people with high risk nmHRPC and people with mHSPC. As stated earlier in this report (section 2.3), the population for nmHRPC differs from that in the NICE scope, which included all adults with nmHRPC. However, the marketing authorisation for apalutamide is for those at high risk of developing metastatic disease, as per the SPARTAN registration trial. The populations used in the model are based on the characteristics of patients in the SPARTAN and TITAN trials (shown in CS Table 7 and Table 8). Clinical advice to the ERG is that the populations in the clinical trials were broadly similar to those seen in UK clinical practice.

As noted earlier, the CS does not define the factors that determine whether a person would be fit enough to receive docetaxel. Prior docetaxel use was a stratification factor in the trial's analysis, with 11% of randomised patients previously receiving docetaxel. Around a nine per cent of patients received docetaxel as a subsequent therapy. Thus, it appears that at a small proportion of patients were fit enough to take docetaxel. However, the ERG notes that is not clear what proportion of patients, if any, in the TITAN trial could be considered ineligible to receive docetaxel.

This is important because survival estimates from the ITT population of TITAN (which appears to include some patients fit enough to take docetaxel, and, presumably, some who were not fit enough for docetaxel) inform the cost effectiveness results for the docetaxel eligible population *and* the docetaxel ineligible population groups. An implicit assumption, therefore, is that the results of TITAN are also applicable to patients ineligible to take docetaxel (i.e. the direct comparison of apalutamide plus ADT versus ADT only).

It is not clear whether the clinical effectiveness of apalutamide differs according to docetaxel eligibility/ineligibility as no such subgroup analysis was presented in TITAN. The ERG notes that a similar issue was discussed recently in the NICE appraisal of abiraterone for the treatment of mHSPC (ID945). The final appraisal determination (FAD) states that "The committee was not presented with evidence of abiraterone's effectiveness in people who

cannot take docetaxel. Without this evidence, it could not say whether abiraterone would be safe or effective in this group" (page 5).

The abiraterone FAD also cites the NHS England commissioning policy which states the following factors indicative of a patient being unfit for docetaxel: 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. In addition, it states that docetaxel should be used with caution in people with a WHO performance status of 2, and that there are few absolute contraindications for docetaxel therapy. Of these factors the ERG is only able to discern the (ECOG) performance status scores of TITAN patients, which were almost exclusively in the range of 0 to 1 (as per the eligibility criteria), thus not meeting the NHS England performance status criterion to be considered as unfit for docetaxel treatment. The ERG acknowledges that criteria to determine fitness for docetaxel may vary between treatment centres and that the decision to offer docetaxel is also informed by the circumstances of the individual patient (e.g. age, co-morbidities, extent of disease) and their preferences. Thus, any attempt to dichotomise TITAN patients into docetaxel eligible and ineligible groups may be imprecise. For this reason the applicability of the results from TITAN to a patient population ineligible for docetaxel is uncertain.

One other factor to note is that the majority of patients in TITAN were newly diagnosed metastatic patients, as opposed to progressing to metastases from local disease. Evidence suggests that these patients have a poorer prognosis than primary progressors. This needs to be taken into account in assessing the applicability of the results of the cost effectiveness analysis to other populations.

ERG conclusion

The patient populations in the economic model appropriately reflect the licensed indications for apalutamide and the clinical trial populations. However, survival estimates from the TITAN trial inform the cost effectiveness results for both the docetaxel eligible population and the docetaxel ineligible population groups. There is evidence that a proportion of patients in TITAN were/had previously been eligible to receive docetaxel, but there is no evidence to suggest whether any patients were ineligible to receive docetaxel. It is therefore uncertain whether the implicit assumption that the results of TITAN are also applicable to patients ineligible to take docetaxel is valid.

4.2.4 Interventions and comparators

The intervention of interest is apalutamide, administered orally as a single daily dose of 240 mg (4x60 mg tablets), in combination with ADT.

The comparators included in the company's base case are:

- For nmHRPC: ADT only;
- For mHSPC: ADT only, and docetaxel and ADT (in patients who can tolerate docetaxel).

For mHSPC, other possible comparators are listed in the NICE scope: abiraterone with prednisone or prednisolone and ADT; and enzalutamide with ADT. These treatments are currently subject to ongoing NICE appraisal and therefore are not considered eligible comparators.

ERG conclusion

The ERG agrees with the comparators selected by the company for the current appraisal.

4.2.5 Perspective, time horizon and discounting

The company includes all direct health effects of treatments. Costs are estimated from the NHS and Personal Social Services (PSS) perspective. Costs and outcomes are discounted at 3.5% in the base case and at 0% and 6% in deterministic sensitivity analysis.

In the base case, the model outcomes are estimated over a lifetime horizon (32 years). Alternative time horizons of 10, 20 and 30 years are considered in scenario analyses (CS Tables 95, 96 and 97). Changing the time horizon to 10 years leads to a significant increase in the ICER. The ERG notes that previous NICE appraisals for prostate cancer (TA259

TA391, TA316 and TA377) applied a 10-year time horizon, however they were focused on the mHRPC setting, in which the disease is more advanced, and it is expected that patients experience lower survival.

ERG conclusion

The company adopted an appropriate perspective, used recommended discounting rates and an appropriate time horizon, which are in line with the NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

4.2.6.1 Clinical efficacy inputs: overview

The company presents their approach to survival analysis and selection of clinical inputs for the economic model in CS section B.3.3.2. As mentioned earlier, the company considered adjusting survival estimates from both SPARTAN and TITAN trials for 'indirect switching', to reflect the one-novel-therapy-commissioning policy in England, as well as for crossover from placebo plus ADT to apalutamide plus ADT, or 'direct' switching, in SPARTAN.

The suitability of the following adjustment methods proposed in the NICE DSU TSD 16[28] was explored:

- Rank Preserving Structure Failure Time Models (RPSFTM)
- Iterative Parameter Estimation (IPE)
- Two-stage method
- Inverse Probability of Censoring Weights (IPCW)

The MFS and rPFS, PFS2 and OS estimates were fitted with parametric models (the proportional hazards-based exponential, Weibull and Gompertz, and the accelerated failure time-based log-normal, log-logistic and generalised gamma) and extrapolated for the model time horizon. Two approaches were considered:

- Fitting independent models to each treatment arm
- Fitting a dependent model in which placebo curve is used as a reference

The most appropriate approach was chosen by investigating whether the assumption of proportional hazards (PH) was reasonable. This was done by inspecting the log-cumulative hazard plots and was supported by assessment of Schoenfeld plots and the Schoenfeld test.

The parametric models were assessed based on their clinical plausibility, consistency with the other survival curves selected for the analysis, and goodness-of-fit statistics (AIC and BIC scores).

Table 34 below provides an overview of survival estimates utilised in the company's base-case and scenario analyses. As shown in the table, the estimates from TITAN were not adjusted: adjustment for novel therapy was explored but not included in the cost-effectiveness analysis because, as the company stated, the adjusted analysis failed to demonstrate any significant impact on survival outcomes and gave counter-intuitive results in some scenarios (see section 4.2.8.2 below); as for crossover to apalutamide, the TITAN data used to inform this submission does not cover the trial period post-unblinding and, as such, is not affected by confounding due to crossover (see section 3.2.6.4 above).

We describe and critique the company's approach in sections 4.2.7 and 4.2.8.

Table 34 Survival estimates used in the company's base-case and sensitivity analyses

Outcome measure	Base case	Scenario(s)
Apalutamide plus ADT versus ADT alone: nmHRPC (SPARTAN trial)		
MFS	Independently modelled using Weibull distributions (both arms)	Independently modelled: log-logistic or log-normal (both arms)
PFS2	Jointly modelled with Weibull distributions fitted to data adjusted for novel therapy restriction and crossover[a]	- Log-logistic, log-normal or generalized gamma - Unadjusted for treatment switching - Independently modelled
OS	Jointly modelled with Weibull distributions fitted to data adjusted for novel therapy restriction and crossover[a]	- Generalized gamma - Unadjusted for treatment switching - Independently modelled
Apalutamide plus ADT versus ADT alone: mHSPC (TITAN trial)		
rPFS	Independently modelled with Weibull distributions fitted to data unadjusted for novel therapy restriction	- Exponential, log-logistic or log-normal - Jointly modelled

Outcome measure	Base case	Scenario(s)
PFS2	Jointly modelled with Weibull distributions fitted to data unadjusted for novel therapy restriction	NA
OS	Independently modelled with Weibull distributions based on 'informed fits' approach,[38] unadjusted for novel therapy restriction	- Log-normal, log-logistic, generalised gamma or Gompertz - Jointly modelled not using 'informed fits'
Apalutamide plus ADT versus docetaxel plus ADT: mHSPC (Bayesian NMA)		
rPFS	Weibull distribution and HRs from Bayesian NMA	Exponential, log-logistic or log-normal
PFS2	Weibull distribution and HRs from Bayesian NMA	NA
OS	Weibull distribution and HRs from Bayesian NMA; informed fits	- Log-normal, log-logistic, generalised gamma or Gompertz - Unstratified fits

NA not applicable
a Survival estimates adjusted for treatment switching using a 'modified' RPFSTM following Diels et al.[29]
Note: When survival estimates are modelled jointly, the proportional hazards assumption is made, and survival in the treatment arm is estimated by applying HR to the parametric curve selected for the comparator arm used as reference. When survival estimates are modelled independently, parametric models are fitted separately to both treatment and comparator arms.

4.2.6.2 Methods of adjustment for treatment switching

The company followed Diels et al.[29] when considering adjustment of the survival estimates for treatment switching. The source appears to be a conference abstract. The company confirmed in clarification response B10 that the approach proposed in Diels et al.[29] has not yet undergone the peer-review process.

The objective of the approach described in Diels et al.[29] was to estimate the OS benefit of apalutamide in SPARTAN by adjusting for subsequent exposure to abiraterone and enzalutamide. The authors stated that their approach was similar to **RPSFTM** but was using (external) patient-level data from COU-AA-302, a randomized-trial comparing abiraterone acetate plus prednisone versus prednisone in mCRPC, to adjust for the survival benefit of the subsequent novel therapies. The COU-AA-302-patient population was matched to the subgroup of metastatic patients with subsequent therapy from SPARTAN using Inverse Probability Weighting (IPW) approach, and the adjusted HR was estimated based on the

counterfactual re-censored survival times. The 'modified' RPFSTM approach is further described in section 4.2.7.2 below.

Diels et al.[29] and the company argue that the 'modified' RPSFTM approach does not require the standard assumptions of RPSFTM, IPCW and two-stage method,[28] and that these assumptions were not valid for SPARTAN. Here, we outline the company's argument. For further details refer to CS Appendix R.1 pages 844-846.

The company states that RPSFTM is typically applied when only the relative treatment effect of one active therapy versus control needs to be estimated based on the trial data; the main assumption of this method is that the benefit of the treatment is equal in patients exposed to it later in time and patients initiated on this therapy earlier (the common treatment effect assumption). The argument goes that the same approach can be applied in a setting with switching to more than one active therapy, with separate acceleration factors for those therapies, but estimation of these multiple parameters reliably from data collected in one trial would not be possible due to data limitations. The company states that the same limitations would also hold for the **IPE** approach which is conceptually identical to RPFSTM.

Another approach, **IPCW**, was not deemed to be valid for the nmHRPC indication (SPARTAN) because, as the company states, it produced counter-intuitive and clinically implausible results, with the survival estimates in the apalutamide arm shifting upwards (see a detailed argument in CS Appendix R page 846). This method, however, was considered suitable for mHSPC but was not used in the company's base-case and sensitivity analyses because of a low proportion of patients who had more than one novel therapy in the TITAN trial (see section 4.2.8.2).

The two-stage method was judged not to be applicable either because of insufficient data to estimate multiple parameters or to sufficiently account for time varying confounding. The method also requires a secondary baseline at the time of switching, which may not be true for SPARTAN and TITAN, because the time between progression and/or discontinuation of randomized treatment and treatment switching was long in a subset of patients in the placebo arm (as illustrated in CS Appendix R Figures 84 and 85 (SPARTAN), and 92 and 93 (TITAN). The additional company's argument is that conducting a reliable analysis for SPARTAN would be challenging as data would be taken from IA1 for MFS whereas OS and PFS2 data would be based on the final analysis set to provide the longest available follow-up.

The appropriateness of adjusting different survival estimates for treatment switching is discussed in sections 4.2.7 and 4.2.8 below.

ERG conclusion

- The novel therapies (abiraterone or enzalutamide) received by patients in the pivotal trials who were randomized to apalutamide would not be available in clinical practice to patients who have already received apalutamide. Our clinical advisors clarified that this is due to potential cross-resistance between treatments and, therefore, these patients, if eligible for subsequent active therapy, will require a different treatment modality (such as radium or chemotherapy). Also, the restriction of not using abiraterone or enzalutamide as subsequent treatment would apply not only if patients had received apalutamide for mHSPC but also if patients had previously received apalutamide for nmHRPC.
- The '**modified' RPSFTM** approach used by Diels[29] requires a number of assumptions: (1) that there would be a similar OS benefit post-metastasis between ADT and prednisone, and (2) a similar OS benefit post-metastasis between abiraterone and enzalutamide in both arms in SPARTAN and TITAN. Our experts consider these assumptions reasonable. This is also confirmed by literature. In a meta-analysis reported by Sathianathen et al.,[39] abiraterone plus ADT and enzalutamide plus ADT in mHSPC were found to be statistically comparable to each other, with HR=1.3 (95% CrI 0.91, 1.9) when using enzalutamide as a reference.
- Another implicit assumption in the company's analysis is that the efficacy of novel therapy is not impacted (decreased) by prior exposure to any other novel therapy. According to clinical advice to the ERG, it is unclear how effective enzalutamide and abiraterone would be following earlier use of apalutamide, but cross-resistance is likely to apply. This is also supported by literature. Antonarakis,[35] reports that patients who receive enzalutamide or abiraterone as first-line therapy and subsequently become resistant have only a 15% to 30% rate of response to the alternative agent as second-line CRPC treatment. Therefore, using evidence from COU-AA-302 (where enzalutamide and abiraterone were used first-line) to adjust for novel therapies not available in the NHS is likely to underestimate the effectiveness of apalutamide.
- We note that evidence from the COU-AA-302 trial was used in NICE TA387 of abiraterone for treating mHRPC not previously treated with chemotherapy.[40] Although COU-AA-302 included only 9% of patients from the UK, it was considered to be generalisable to clinical practice in England, and the trial population

representative of patients who would be offered abiraterone; the life expectancy of people in the comparator arm of COU-AA-302 reflected that of patients in the NHS because the subsequent active treatments in this arm were similar to those patients receive in clinical practice.

- We note that COU-AA-301 trial was also included in NICE TA387, but patients in the COU-AA-302 trial appear to be a better match to SPARTAN trial participants (see Appendix 9.2). We, therefore, consider that using external data from the COU-AA-302 trial for novel therapy adjustment would be appropriate because after progression (post-metastasis in SPARTAN, and post-radiographic in TITAN) patients from both pivotal trials were quite similar to those in COU-AA-302, and the treatment effect modifiers were adjusted for (for a further discussion see sections 4.2.7.2 and 4.2.8.2).
- It is unclear, however, whether the survival estimates from COU-AA-302 had been adjusted for crossover in that trial when estimating the shrinkage factors for novel therapy in SPARTAN and TITAN. We note that in the company's submission for the NICE TA387, survival estimates were not adjusted for crossover, but this was done in an additional analysis on request from the NICE appraisal committee. Therefore, if the COU-AA-302 estimates used in the 'modified' RPFSTM had not been adjusted for crossover, the clinical effectiveness of apalutamide is likely to be overestimated.
- The implementation of the 'modified' RPFSTM approach could not be independently verified because the IPD from the pivotal trials were not available to the ERG (see clarification question response B6).
- The company's argument against using the **two-stage** method because of lack of MFS data at the final analysis stage is not supported by the evidence because MFS had already been mature at IA1 cut-off date (see Figure 3). We agree, however, that using the two-stage approach would have a caveat because of the switching mechanism in SPARTAN which was based on the trial data.[28]
- The **IPCW** analysis, which was not included in CS, was requested by the ERG but not provided (see clarification response B8). Therefore, the suitability of this method to adjust for treatment switching in SPARTAN could not be established.

4.2.7 Survival curves: nmHRPC

Clinical effectiveness evidence for nmHRPC was sourced from the SPARTAN trial.[22] SPARTAN provided MFS, PFS2, and OS data (see section 3.2.5).

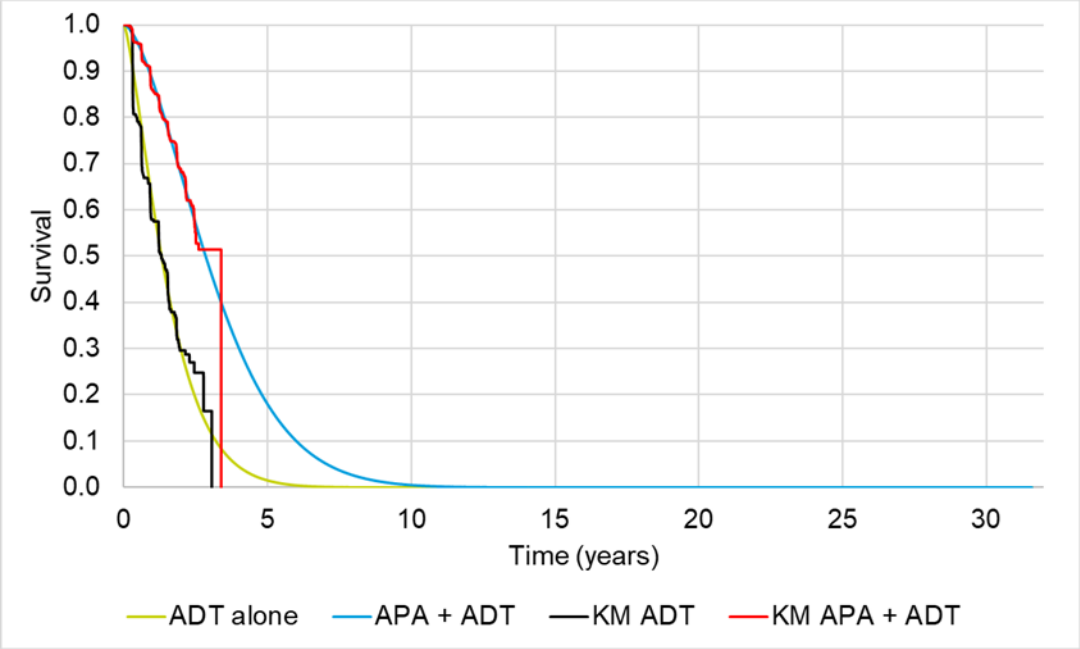


Figure 15 Metastases-free survival: nmHRPC

Source: prepared by the ERG using the company's model

4.2.7.1 Metastases-free survival (MFS): nmHRPC

Pre-progression in the nmHRPC population is modelled using MFS estimates as a proxy for clinical progression (CS Table 53). Based on the log-cumulative hazard plot for MFS (CS Figure 41) and the Schoenfeld test used to assess the proportionality of hazards (PH), the company concluded that the PH assumption did not hold: the curves were not parallel over the entire follow-up period, and the Schoenfeld test produced a significant p-value (p=0.0118). Therefore, standard parametric models were fitted independently to the MFS data for each treatment arm. CS Figure 42 shows the extrapolated curves for the treatment and comparator arms along with the Kaplan–Meier estimates from the SPARTAN trial. Summaries of the goodness-of-fit statistics and MFS estimates over time are shown in CS Table 56.

The company concluded, based on clinical advice and AIC and BIC criteria (CS Table 56), that on balance, the Weibull models (shown in Figure 15) were the most clinically plausible for the extrapolation of MFS in both treatment arms (a detailed argument is presented in CS page 180). Therefore, these curves were applied in the company's base case, with log-logistic and log-normal tested in scenarios (see Table 34).

ERG conclusion

- In the company's analysis, MFS was not adjusted for crossover to apalutamide. We note that the Kaplan-Meier curve for the ADT arm in SPARTAN was mature

at the IA1 cut-off date when the study was unblinded (see Figure 3 above) and, therefore, adjustment for crossover was not needed.

- Expert advice to the ERG suggests that none of the parametric forms used in the company's analysis adequately capture MFS: the selected models underestimate MFS in the ADT arm at 5 and 10 years, except generalised gamma which has a clinically implausible long tail, but may be overestimating it in the apalutamide arm. Therefore, using more flexible models, such as piecewise parametric models, would be more appropriate.[41]
- We assume the Weibull fits in the ERG base case, and test the structural uncertainty around the parametric distributions by applying log-logistic and log-normal models independently fitted to the observed data (see section 6.3 below). We also note that Kaplan-Meier data in SPARTAN were mature and, therefore, we conduct an additional scenario applying these estimates (as explained in section 6.3).

4.2.7.2 Second progression-free survival (PFS2): nmHRPC

4.2.7.2.1 PFS2 adjustment for treatment switching: nmHRPC

The 'modified' RPFSTM approach used by the company to adjust PFS2 from SPARTAN for treatment switching is outlined below. For a detailed explanation refer to CS Appendix R page 847.

STEP 1: Run g-estimation to estimate the shrinkage factor for abiraterone/enzalutamide, exp(ψ^{ST}), from COU-AA-302 using ATT weights to match the COU-AA-302 population to SPARTAN switching population.

STEP 2: Estimate shrinkage factor for apalutamide:

2.1: Estimate counterfactual survival time (in both treatment arms) adjusted for subsequent therapy with abiraterone/enzalutamide by applying the shrinkage factor derived in step 1.

2.2: Apply RPSFTM to estimate the shrinkage factor for apalutamide, exp(ψ^{a}), using counterfactual survival time from step 2.1.

STEP 3: Estimate counterfactual survival time (with or without re-censoring) following the UK one-novel-therapy rule using the estimated shrinkage factor for abiraterone/enzalutamide derived in step 1 and for apalutamide in step 2.

Here it is assumed that once patients switched to a non-permitted subsequent therapy, they remain on that therapy from the time of switch until they experience a PFS2 event.

The effect of re-censoring of the counterfactual surviving times on the shrinkage factors was estimated (as described in Appendix 9.3): in a Cox PH regression model, applied to the counterfactual survival times, HRs for RPSFTM analyses with and without re-censoring were [redacted] and [redacted], respectively (CS Appendix R Table R.9). We note that the HR in the ITT analysis was 0.553.

ERG conclusion

- In a simulation study conducted by Latimer et al.,[42] RPSFTM with re-censoring consistently overestimated effectiveness of the active treatment and produced a higher bias when compared with RPSFTM without re-censoring. We note, however, that Latimer et al.[42] considered performance of the RPFSTM adjusting for switching from control to active arm only, and therefore, the results of this simulation study might not be directly applicable to the 'modified' RPFSTM approach with two different types of adjustment for treatment switching. Hence, it is not clear which of the approaches to re-censoring, undertaken in the 'modified' RPFSTM, is likely to be less biased.
- The estimates applied in the company's economic analysis were obtained without re-censoring. Conducting an additional analysis with re-censoring is also recommended (see Latimer et al.[42]) because, as explained above, it is not clear whether the analysis without re-censoring would result in a smaller bias.

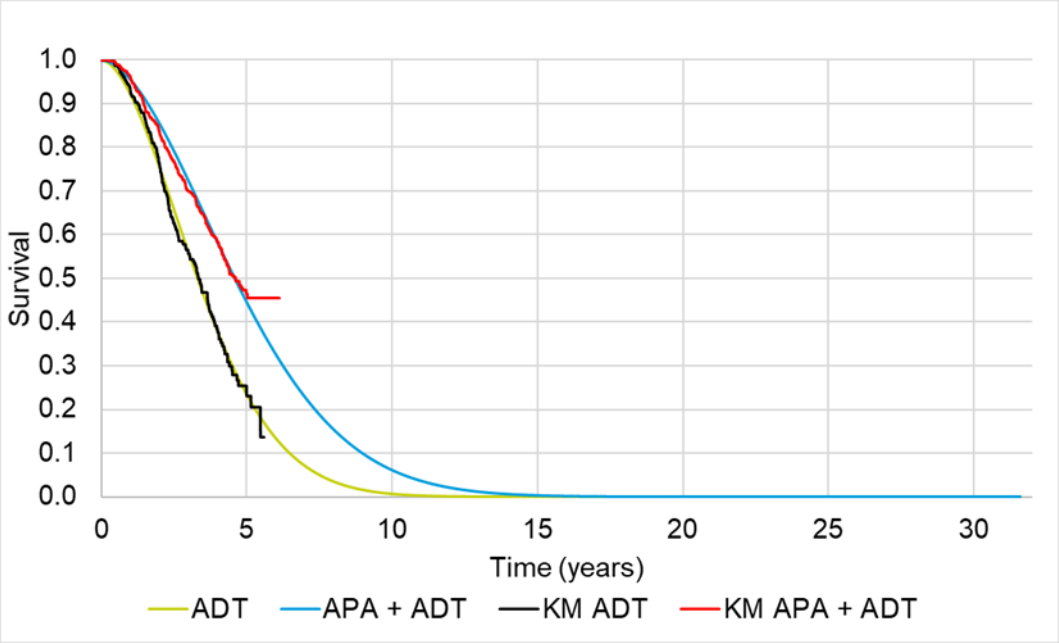


Figure 16 PFS2: nmHRPC

Source: prepared by the ERG using the company's model

4.2.7.2.2 PFS2 extrapolations: nmHRPC

The log-cumulative hazard plots for PFS2 (CS Figure 46) show that the curves remain relatively parallel over time for data adjusted for the one-novel-therapy restriction and crossover. Therefore, the company concluded that the PH assumption held, and that it would be appropriate to apply jointly fitted models in the base case. We note that the log-cumulative hazard plot for unadjusted data (CS Figure 46) also suggests proportionality.

The company fitted six parametric distributions to the adjusted PFS2 Kaplan–Meier data for the placebo arm and applied a hazard ratio for the apalutamide arm (CS Figure 47). Based on the statistical fits (AIC/BIC scores), the log-logistic, lognormal and generalized gamma distributions had the best fits to the adjusted PFS2 data (CS Table 58).

The Weibull models (shown in Figure 16), selected by the company for extrapolation of the PFS2 data, were considered to be most clinically plausible. We note, however, that they have average AIC and BIC when compared to the scores for the other models (see CS Table 58). The use of the log-logistic, lognormal and generalized gamma distributions was explored in scenarios along with the impact of using unadjusted data (see Table 34 and section 5.2). The full argument is presented in CS section B.3.3.5.2 page 190.

ERG conclusion

- The ERG adopts the company's approach to modelling PFS2 in the base case and scenario analyses (see section 6 below).

- The PFS2 estimates for the apalutamide arm in SPARTAN were relatively immature (see Figure 16), which is likely to contribute to the uncertainty in the economic outcomes.

4.2.7.3 Overall survival (OS): nmHRPC

4.2.7.3.1 Historical OS data: nmHRPC

The company considered using external data for modelling OS from the SPARTAN trial following the 'informed fits' approach proposed by Pennington et al.[38]

The underlying assumption of this method is that the shape parameter of any parametric distribution is a study independent parameter and could be used from external data to inform the shape parameter for the new clinical trial. The temporal bias between the trials can be adjusted for by applying a relative treatment effect. This means that the hazards between the historical and the SPARTAN trial ADT arms need to be proportional.

The company conducted an exploratory analysis using external data from three trials identified in a systematic review.[43] Kaplan–Meier curves for the placebo arms of the three studies were digitized, and individual patient data (IPD) datasets were created using methodology described by Guyot et al.[44] The reconstructed IPD from the studies were used to create a pooled Kaplan–Meier placebo curve. It is shown in CS Appendix S.2 Figure 104 along with the adjusted placebo arm from SPARTAN. A survival comparison between the historical trials and the SPARTAN trial (adjusted OS) is presented in CS Appendix S.2 Table S.4.

The PH assumption was visually assessed with a log-cumulative hazards plot (see CS Appendix S.2 Figure 105) and statistically tested with the Schoenfeld test. Based on visual assessment, the curves are parallel, and the proportional hazards assumption was considered to hold. This was further confirmed by the Schoenfeld test which was not significant (p=0.267).

As the PH assumption between the SPARTAN trial and the historical ADT arm held, the historical ADT arm data was included as a third arm in addition to apalutamide and placebo arms from the SPARTAN trial. In the model fitting, apalutamide and placebo were used as covariates to define the treatment effect compared to the historical clinical trial ADT arm.

The company concluded that given the limited number of historical ADT OS data available from literature and the fact that SPARTAN had longer follow-up than the studies identified in

the systematic review, the 'informed fits' approach[38] was not carried through into the modelling.

ERG conclusion

- The company did not utilise the historical ADT arm in the base case because, as the company stated, the 'informed fits' approach[38] was thought to provide only minimal additional benefit, and no exploratory analysis based on the 'informed fits' approach has been provided.
- The ERG critique of the searches conducted by the company for the 'informed fits' approach is provided in Appendix 9.4. Due to limited reporting of the searches, it was not possible to assess whether any relevant studies might have been missed.

4.2.7.3.2 OS proportional hazards (PH) assessment: nmHRPC

CS Figure 51 presents the log-cumulative hazard plot for OS in the apalutamide and placebo arms of the SPARTAN trial. The plot shows that the curves are relatively parallel over time. Based on the Schoenfeld test, the proportional hazards assumption seems to hold, as the resulting p-value was not significant (p=0.7321). Therefore, the company considered it appropriate to apply jointly fitted models in the base case. The company states that the adoption of this approach was supported at an advisory board.[45]

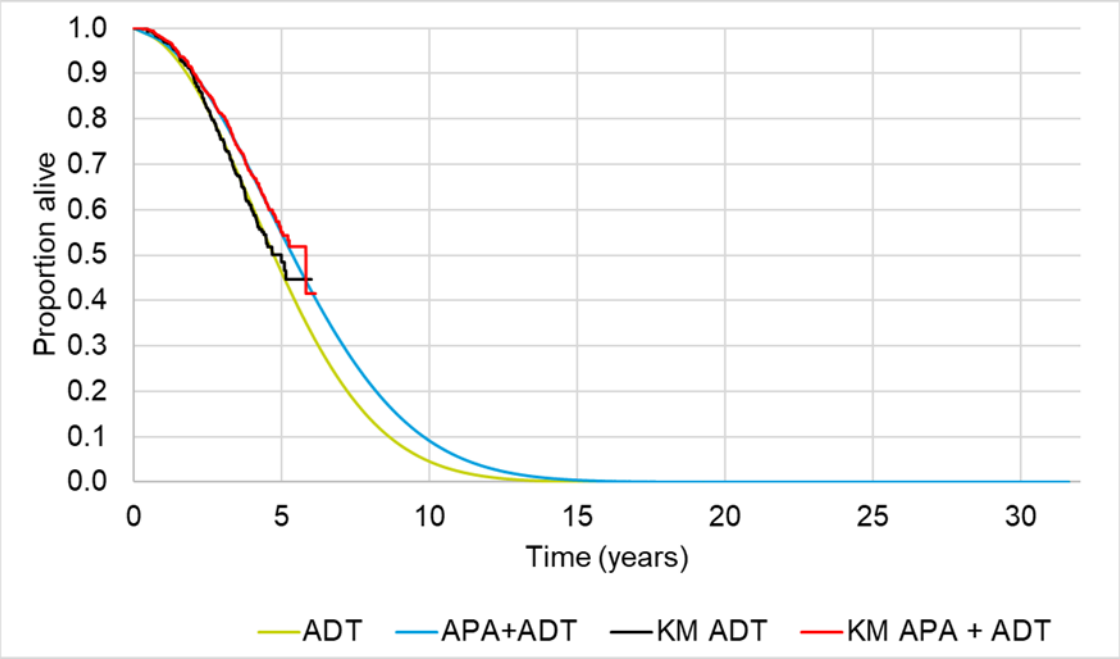


Figure 17 Overall survival: nmHRPC

Source: prepared by the ERG using the company's model

4.2.7.3.3 OS extrapolations: nmHRPC

OS estimates from the SPARTAN trial were adjusted for novel therapy and crossover to apalutamide using the same approach as for PFS2 (see section 0).

Six parametric functions were fitted jointly to the adjusted OS data (see CS Figure 52). The goodness-of-fit statistics and survival outcomes over time are presented in CS Table 60. The company chose the Weibull distribution for the extrapolation of OS because of its clinical plausibility. The use of the generalized gamma distribution, the second statistically best-fitting model, to extrapolate OS was explored in a scenario analysis (Table 34).

ERG conclusion

- The assumption that PH would hold in the extrapolated part of the survival curves could not be verified due to lack of evidence. We note that the survival estimates from SPARTAN, on which the PH assumption was tested, were immature (see Figure 4). Therefore, using models fitted to the treatment arms separately would be more appropriate, because this approach does not require the PH assumption which may be clinically implausible.[46] We note, however, that this assumption seems to have only a moderate impact on the results based on the drug list prices, and does not change the outcome of the cost-effectiveness analysis (see section 6.3).
- We have been advised that both Weibull curves used in the company's base case are likely to underestimate the overall survival at 10 years, and possibly 15 years (see CS Figure 52). Based on this advice, we select the fitted jointly generalised gamma models (shown in Figure 17) for our base case. These models have a good visual fit to the Kaplan-Meier estimates from SPARTAN, and lower AIC and BIC scores when compared to the Weibull models (see CS Table 60). In scenarios, we test the independently fitted generalised gamma and jointly fitted Weibull curves (section 6.3).

4.2.8 Survival curves: mHSPC

For mHSPC, the comparison of apalutamide plus ADT to placebo plus ADT was made using head-to-head data from the TITAN trial (see section 3.2.6). The extrapolation of rPFS, PFS2 and OS data, and the novel therapy adjustment of PFS2 and OS estimates, considered by the company, are outlined in sections 4.2.8.1 – 4.2.8.5. Note that crossover from placebo to apalutamide was not present in the TITAN data used in this appraisal and, therefore, this type of adjustment was not implemented.

The comparison of apalutamide plus ADT to docetaxel, informed by the NMA (critiqued in sections 3.3 and 3.4) is described in section 4.2.8.6 below.

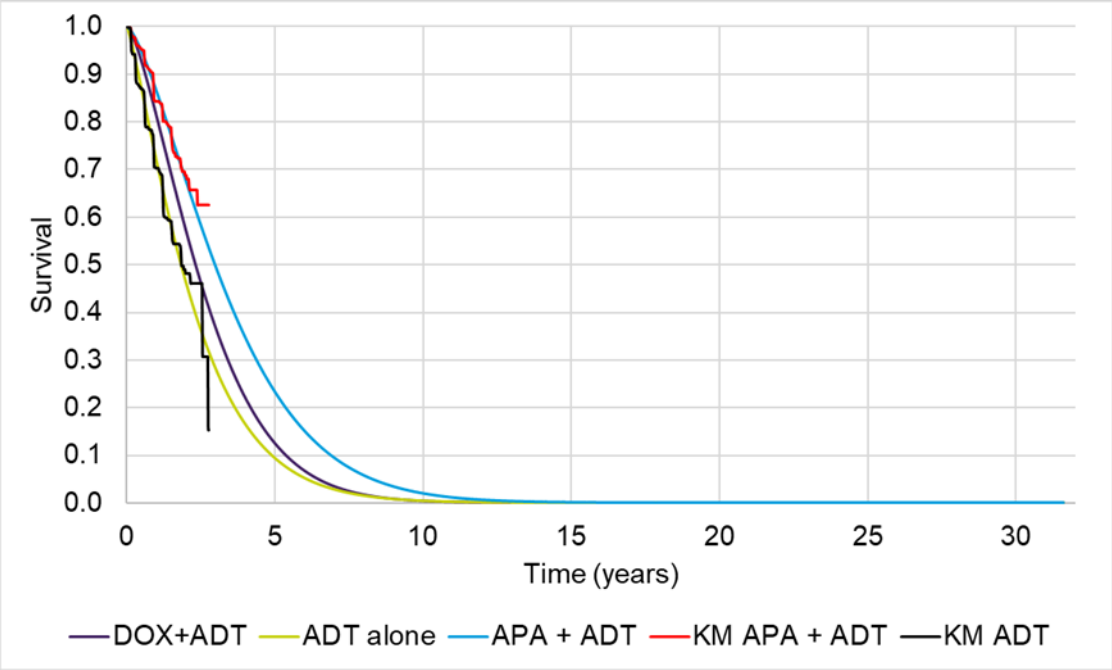


Figure 18 Radiographic progression-free survival: mHSPC

Source: prepared by the ERG using the company's model

4.2.8.1 Radiographic progression-free survival (rPFS): mHSPC

In the company's model, rPFS was considered as a proxy for clinical progression in mHSPC. PFS2 data from the 23rd November 2018 data cut of the TITAN trial were used in the company's analysis (Figure 9).

The log-cumulative hazard plot for rPFS (CS Figure 43) and Schoenfeld test (p=0.0586) indicate that the PH assumption may be violated. Given this assessment, the company concluded that parametric curves should be fitted for apalutamide and placebo independently.

Six parametric functions were fitted to the rPFS data from TITAN (see CS Figure 44 and CS Appendix J.1). Summaries of the goodness-of-fit statistics and the predicted survival over time are presented in CS Table 57. Based on clinical advice, Weibull curves (Figure 18) were selected for the company's base case, and exponential, log-logistic and generalized gamma were tested in scenarios (see sections 5.1 and 5.2).

ERG conclusion

- The Kaplan-Meier curves for the apalutamide arm in TITAN were highly immature (see Figure 18) which is likely to contribute considerably to the uncertainty in the cost-effectiveness of apalutamide for this indication, because the model predictions are sensitive to variations in rPFS.
- On balance, we apply the same models, Weibull, for our base case. We note, however, that the Weibull models have higher AIC and BIC scores compared to the log-logistic models. Besides, based on clinical advice, the Weibull fits are likely to underestimate the proportion of ADT patients radiographic-progression-free at 5, 10 and possibly 15 years.
- We note, however, that the historical ADT arm with a follow-up of about 9 years (discussed in section 4.2.8.5.2 below) appears to have a rather complex hazard function increasing during the first three years which correspond to the follow-up in TITAN (see Figure 21). If the shapes of the hazard functions for rPFS and OS are likely to be similar, more flexible models for rPFS which could accommodate complex hazard functions, such as piecewise models, would be required because none of the parametric models considered in the CS would be suitable. We note that only Weibull and Gompertz have increasing hazards (see CS Appendix Figure 49). However, the assumption that rPFS and OS are likely to have similarly shaped hazard functions might be too strong, and it can be proved, or disproved, only by more extended follow-up data.
- We test the other parametric distributions in scenarios reported in section 6.3.

4.2.8.2 Second progression-free survival (PFS2): mHSPC

In TITAN, 5% of patients randomised to apalutamide received novel therapies as first subsequent treatments (see CS Table R.11). Therefore, the company considered adjusting PFS2 and OS survival estimates for the impact of having more than one novel therapy, as outlined in sections 4.2.8.3 and 4.2.8.5.1 below. For further details refer to CS Appendix R.3.

4.2.8.3 PFS2 adjustment for novel therapy: mHSPC

PFS2 data from the 23rd November 2018 data cut of the TITAN trial was utilised in the company's analysis. Two methods, **IPCW** and the 'modified' **RPSFTM**,[29] were considered to adjust for biases introduced by the use of novel therapies not available in the NHS.

The implementation of the 'modified' RPSFTM method[29] was similar to that in SPARTAN, with the only exception that the propensity score-based approach used to match the COU-

AA-302 population to the SPARTAN switching population was not implemented for TITAN because, as stated in the submission, “impact for SPARTAN was limited, and there was no indication that this would be different for TITAN”. The shrinkage factor for abiraterone/enzalutamide estimated for SPARTAN population in step 1 (see section 4.2.7.2.1) was applied in the following steps when estimating counterfactual survival times for TITAN.

Regarding IPCW (described in CS Appendix R.3.2 page 872), the company stated that “the IPCW method assumes no unmeasured confounders related to both baseline and time-dependent patient characteristics; although this assumption cannot be tested, most clinically relevant prognostic factors available in the trial were included in the statistical modelling”. Baseline and time-varying covariates used in the analysis are shown in CS Appendix R.3.2 Table R.13.

The adjusted PFS2 Kaplan-Meier curves for apalutamide obtained using IPCW and RPSFTM (without re-censoring) are shown in CS Appendix R.3.3 Figure 97 along with apalutamide and placebo Kaplan-Meier curves from the ITT analysis.

The resulting HR estimates based on RPSFTM with and without re-censoring were [redacted] and [redacted], respectively (CS Appendix R.3.3 Table R.15). In the RPFSTM propensity-score-based analysis (requested by the ERG), the respective estimates were [redacted] and [redacted] (see clarification response B12).

The HR derived using IPCW was [redacted] (CS Appendix R.3.3 Table R.15).

We note that HR in the ITT analysis was 0.657 (CS Appendix R.3.3).

We discuss the appropriateness of the novel therapy adjustment for PFS2 in section 4.2.8.5.1 below.

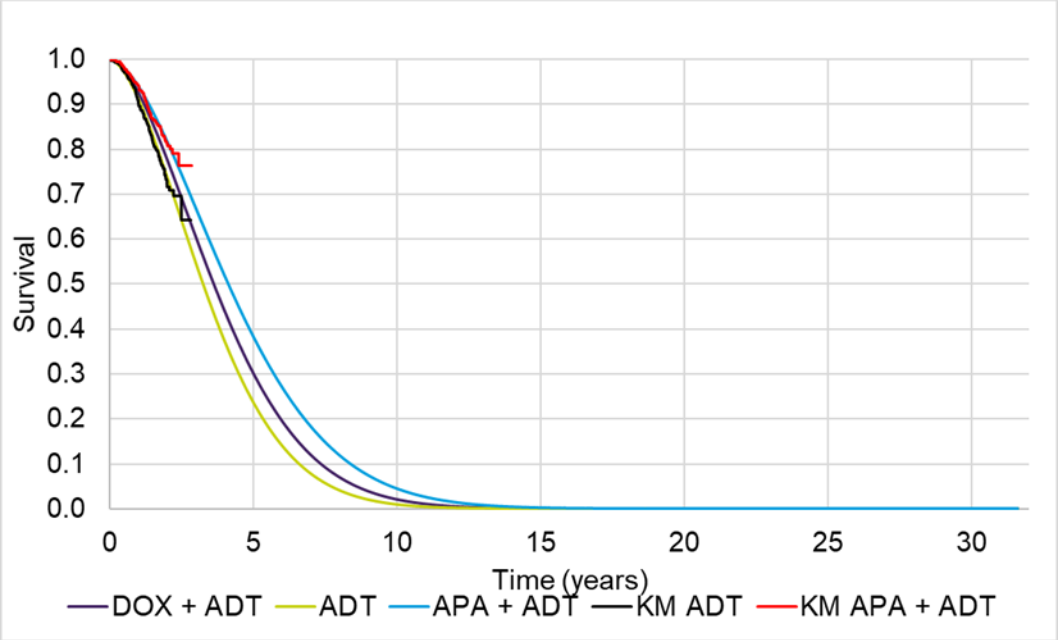


Figure 19 Second progression-free survival: mHSPC

Source: prepared by the ERG using the company's model

4.2.8.4 PFS2 extrapolations: mHSPC

PFS2 data unadjusted for the one novel agent restriction were used for PH assessment. The log-cumulative hazard plot (CS Figure 48) shows that the curves remained relatively parallel over time. Therefore, the company concluded that the PH assumption held, and that it was appropriate to apply jointly fitted models in the base case, with the placebo arm as the reference curve.

Fitted parametric distributions are shown in CS Figure 49 and CS Appendix J.1. We note that the Weibull and Gompertz models have the lowest AIC and BIC scores (see CS Table 59). The Weibull fits applied in the company's base case (see Figure 19) were selected on the basis of clinical plausibility and consistency with the curves for rPFS and OS (as explained in CS page 194). No sensitivity analyses were conducted to test the uncertainty in these estimates.

ERG conclusion

- We apply the Weibull fits in the ERG base case because of their consistency with rPFS and OS curves. The other plausible models, Gompertz, are tested in a scenario (see section 6).

- We note that the PFS2 estimates in TITAN (Figure 19) were immature and, therefore, the long-term PFS2 extrapolations assuming proportional hazards are likely to be highly uncertain.

4.2.8.5 Overall survival (OS): mHSPC

4.2.8.5.1 OS adjustment for novel therapy: apalutamide plus ADT versus placebo plus ADT in mHSPC

OS estimates from TITAN were adjusted for novel therapy using the same approach as that used for PFS2 (see section 4.2.8.3). CS Appendix R.3.3 Figure 96 shows the adjusted OS Kaplan-Meier curves for both arms obtained using IPCW and RPSFTM (without re-censoring) and those from ITT analyses. CS Appendix R.3.3 Table R.14 provides the respective hazard ratios.

As with PFS2, the COU-AA-302 population was not matched to the TITAN population in the company's RPFSTM analysis. This has been done in an additional scenario (see clarification response B12).

When the COU-AA-302 and TITAN populations were not matched, the HR estimates derived in the analyses with and without re-censoring were [redacted] and [redacted]. The respective HR estimates derived from the propensity-score-based RPSFTM were [redacted] and [redacted]. We note that HR derived from the ITT analysis was 0.671 (Table 22).

The company concluded that the novel therapy analysis failed to demonstrate any significant impact on survival outcomes (see CS Appendix R Figures 96 and 97) and gave counter-intuitive results in some scenarios. Therefore, the unadjusted TITAN data were used in the base-case analysis (Table 34).

As has been mentioned in section 4.2.8.3 with regard to IPCW, the most clinically relevant prognostic factors available in TITAN were included in the statistical modelling (see CS Appendix R.3.2 Table R.13).

ERG conclusion

- The IPCW and RPFSTM exploratory analyses could not be verified because the IPD from TITAN was not available to the ERG.
- We agree that, based on the estimates provided by the company, there seems to be an inconsistency between the HRs derived from the RPFSTM and IPCW analyses adjusting for treatment switching and that for ITT. Therefore, excluding the

adjustment for novel therapy from the base case is reasonable. It is certain, however, that the company's base case ICER was underestimated, because a higher number of patients in the apalutamide arm had non-permitted life-prolonging treatments when compared to the control arm ([redacted]% and [redacted]%, respectively, see CS Table R.11).

4.2.8.5.2 Historical OS data: apalutamide plus ADT versus placebo plus ADT in mHSPC

OS Kaplan-Meier estimates from TITAN were immature (see Figure 10). To reduce uncertainty in the long-term extrapolation of the OS estimates, an 'informed fits' analysis,[38] where historical survival data are used to inform survival extrapolations, was conducted, and the results of this analysis were adopted in the company's base case. The analysis is reported in CS Appendix S.

Seven published studies selected in a systematic literature review (see CS Appendix S.1.1 Figure 98) had longer follow-up relative to that in TITAN. We note that all the selected studies were published after 2013. Kaplan–Meier curves for the placebo arms of these studies were digitized, pseudo-IPD datasets were created[44] and pooled together (see

Figure 20). [redacted]

[redacted] This is discussed in the next section.

On request from the ERG, the pseudo-IPD datasets were provided (see clarification response B11), and we were able to recreate the pooled historical ADT arm (

Figure 20). The hazard function for this arm is shown in Figure 21 below.

Figure 20 OS Kaplan-Meier curve for ADT arm in TITAN versus pooled historical ADT arm

Source: CS Appendix S.1.2 Figure 99

ERG conclusion

- The ERG critique of the searches conducted by the company for the 'informed fits' analysis is presented in Appendix 9.4.
- The implementation and the outcomes of the 'informed fits' approach could not be verified because the IPD were not made available to the ERG.
- We note, however, that based on feedback from the advisory board,[45] current patients in clinical practice would perform better than patients from the historical ADT arm. Therefore, using the historical ADT arm in the economic analysis is likely to increase uncertainty in the economic outcomes.

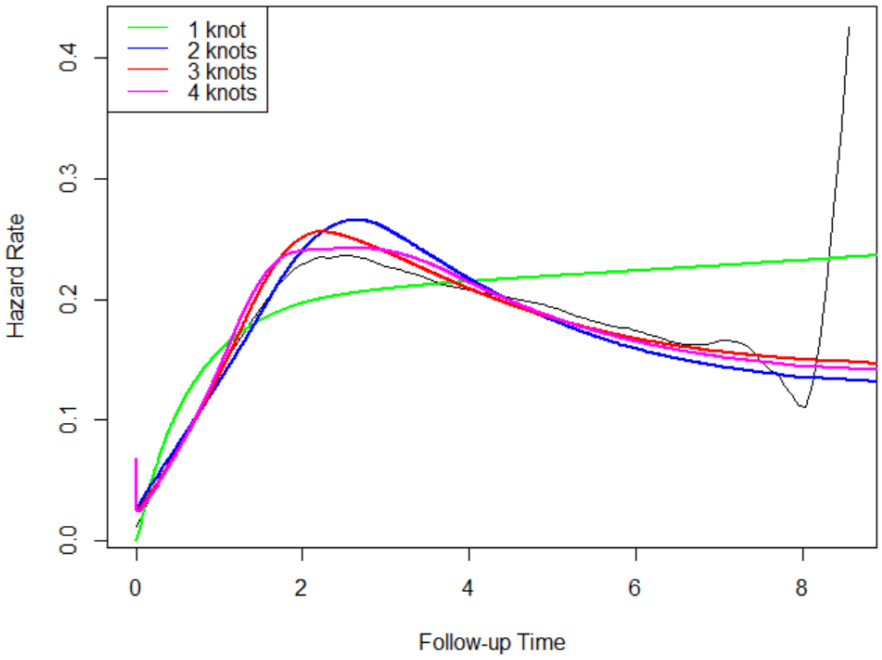


Figure 21 Hazard function for the historical ADT arm

Source: the plot was generated by the ERG using R function flexsurvspline[47] which implements a spline model of Royston and Parmar[48] with 1-4 knots (R version 4.0.2)

4.2.8.5.3 OS proportional hazards (PH) assessment: apalutamide plus ADT versus placebo plus ADT in mHSPC

The log-cumulative hazard plots for apalutamide versus placebo from TITAN, and placebo from TITAN versus the pooled historical ADT data are presented in CS Figure 53. The plots show that the curves remain parallel throughout the trial follow-up. The resulting p-value from the Schoenfeld tests were statistically non-significant (p=0.9803 for apalutamide versus placebo, and p=0.9754 for placebo versus the pooled historical data). Therefore, the company concluded that the assumption of common shape between the curves (required for the 'informed fits' analysis[38]) seemed to hold.

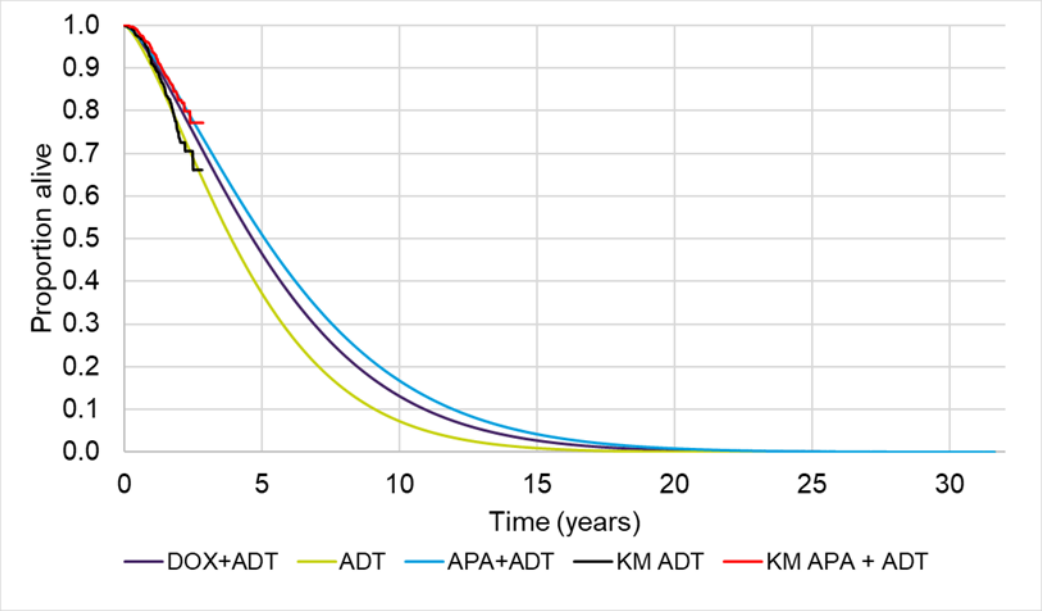


Figure 22 Overall survival: mHSPC

Source: prepared by the ERG using the company's model

4.2.8.5.4 OS extrapolation: apalutamide plus ADT versus placebo plus ADT in mHSPC

Parametric functions fitted to the historical OS 'informed fits' for each treatment arm from the TITAN trial are shown in CS Figure 54 and Appendix J.1. Summaries of the goodness-of-fit statistics and survival estimates over time are presented in CS Table 61. The fitted distributions were validated against overall survival estimates from the external sources identified in the company's literature review (see CS Figure 66 and section 4.2.8.5.2 above). The company states that, based on expert opinion, the Weibull curves (see Figure 22) provided the most clinically plausible extrapolations. They were applied in the company's base case, with the lognormal, log-logistic, generalized gamma and Gompertz tested in scenarios.

ERG conclusion

- The clinical expert from the advisory board[45] noted, when discussing the pooled historical ADT arm, that it would be unusual for patients to die from prostate cancer within a year of diagnosis. We note, however, that all OS parametric curves considered by the company for apalutamide and placebo drop sharply from the very beginning of the observation period (see Figure 22).
- In our expert's opinion, the Weibull models, adopted in the base case, are likely to slightly underestimate patient survival at 5, 10 and possibly 15 years in both treatment arms. The generalised gamma curves, which have lower AIC and BIC

scores than Weibull, appear to be the next most clinically plausible fits, but they have tangibly longer tails. Therefore, on balance, we select the Weibull models (which are more conservative) for the base case and test the other curves in scenario analyses (see section 6.1).

- We note, however, that the OS estimates in TITAN (Figure 19) were immature and, therefore, the long-term extrapolations assuming proportional hazards are likely to be highly uncertain. Moreover, the historical ADT arm (see Figure 20) used in the 'informed fits' approach seems to have a complex hazard function and, therefore, more flexible models are likely to be more appropriate.[41]

4.2.8.6 Comparison of apalutamide plus ADT versus docetaxel plus ADT

The cost-effectiveness analysis for apalutamide plus ADT versus docetaxel plus ADT was based on the HR estimates derived from the Bayesian NMA (see sections 3.3 and 3.4).

The mean HR estimates derived in the NMA were [redacted] for rPFS and [redacted] for OS (Table 26).

To estimate rPFS for docetaxel plus ADT, the respective HR estimate from the NMA was applied to the selected rPFS curve for apalutamide plus ADT. The resulting rPFS is shown in Figure 18 along with the estimates for apalutamide plus ADT and ADT alone.

The OS curve for docetaxel plus ADT (see Figure 22) was derived in the same manner as for rPFS, i.e. using HR from the NMA (Table 26).

PFS2 for docetaxel plus ADT (Figure 19) was estimated using the HR for rPFS, [redacted] as a proxy because PFS2 data were not available for docetaxel plus ADT (see sections 3.3 and 3.4 above).

Some of the trials used in the Bayesian NMA had subsequent novel therapies which would not be available in the NHS. This is discussed in sections 3.3 and 3.4.

According to CS Table 97, OS curve fitting approach in the company's main analysis was based on 'informed fits', and unstratified approach was tested in a sensitivity analysis. The company, however, does not provide any further details on the implementation of the 'informed fits' approach in the comparison of apalutamide with docetaxel.

ERG conclusion

- The company's economic analysis for apalutamide versus docetaxel was based on the clinical efficacy results from the NMA, where adjustment for novel therapy was

not considered. This is likely to increase uncertainty in the ICER for apalutamide versus docetaxel.

- Using the HR estimate for rPFS as a proxy to model PFS2 (as described above) also contributes to the uncertainty in the cost-effectiveness of apalutamide.

4.2.9 Adverse events

The model includes all serious adverse events of grade 3-4 that occurred for any treatment. CS Table 82 reports the incidence of these adverse events. The ERG found some inconsistencies between the values used in the model, the values reported in CS Table 82 and the values presented in the cited sources. Following the ERG clarification question B18, the company acknowledged these discrepancies and provided an updated model with the correct inputs.

The occurrence of adverse events in the pre-progression phase is based on the SPARTAN trial for nmHRPC, on the TITAN trial for mHSPC and on a study by Gravis et al.[49] for the comparison against docetaxel plus ADT. The most frequent grade 3-4 adverse event is neutropenia (32% in docetaxel arm), with the remaining adverse events occurring in less than 17% of patients. For the apalutamide plus ADT arm, the most frequent grade 3-4 adverse event is hypertension (16.3% for nmHRPC and 8.4% for mHSPC).

The occurrence of adverse events in the post-progression phase was informed by relevant clinical trials, which are detailed in CS Table 82. Neutropenia is also the most frequent grade 3-4 adverse event occurring in patients with mHRPC (82% of patients receiving cabazitaxel and 32% receiving docetaxel).

Adverse events were incorporated by using a aggregated per cycle probability of adverse events. In the base case, the impact of adverse events was accounted for by weighted disutilities and costs per patient, as detailed in sections 4.2.10 and 4.2.11.

4.2.10 Health related quality of life

4.2.10.1 Systematic literature review of utility data

The company conducted a SLR to identify HRQoL data for patients with nmHRPC and mHSPC (CS Appendix H). For nmHRPC, the searches were performed in July and August 2018 and the final update search was performed in May and June 2020. For mHSPC the original searches were performed in September 2015 and the final update was in May 2020.

For nmHRPC, seven publications were identified, and these are summarised in CS Appendix H. Of these, two publications fully adhered to the NICE reference case, while four others used the EQ-5D but did not apply a UK tariff. The two publications that met the NICE reference case were the NICE appraisal of enzalutamide for nmHRPC (TA580) and the Scottish Medicines Consortium appraisal of enzalutamide for nmHRPC. The utility values from these publications are shown in Table 35.

For mHSPC, 29 studies were identified (CS Appendix H). None of these studies fully adhered to the NICE reference case – they either did not report utility values or the reported utility values were not estimated using the EQ-5D.

The company did not provide a review of HRQoL in patients with mHRPC and so the ERG requested this (clarification question B15). The company responded that they were unable to obtain all utility values from previous NICE technology appraisals as some data were redacted. This information is provided below in Table 35. The values used in the company's model for second and third-line mHRPC are much lower than in TA377 and TA580. We report scenario analyses using utility values from the NICE appraisals of enzalutamide for nmHRPC (TA377 and TA580) in section 6.

Table 35 Health state utility values for mHRPC from previous NICE appraisals

Appraisal	Utility values
ID945: Abiraterone	High risk mHSPC: 0.792 1L mHRPC: 0.704 2L mHRPC: 0.525 3L mHRPC: 0.420 Note the mHRPC utility values were calculated using the exact same method that is outlined in the response to clarification question B15
TA580: Enzalutamide	1L mHRPC: 0.81[a] 2L mHRPC: 0.8 [a] 3L mHRPC: 0.688 End-of-life utility: 0.590 (applied for 3 months period prior to death)
TA391: Cabazitaxel	mHRPC (stable disease): 0.704-0.819 mHRPC (progressive disease): 0.6266 (until last 3 months of life which are set to 0)
TA387: Abiraterone	1L mHRPC: 0.83 2L mHRPC: 0.625 3L mHRPC: 0.5
TA377: Enzalutamide	mHRPC (stable disease): 0.844 Post progression 1: 0.658 Post progression 2: 0.612 Palliative care: 0.5
TA316: Enzalutamide	mHRPC (Disutility progression): -0.085
TA259: Abiraterone	Pre-progression: 0.780 mHRPC (Post-progression): 0.5
Key: 1L, first line, 2L, second-line, 3L, third-line, mHRPC, metastatic hormone relapsed prostate cancer. [a] Values reported in the Scottish Medicines Consortium appraisal of enzalutamide for nmHRPC	

4.2.10.2 Study-based health related quality of life

HRQoL was measured in the SPARTAN and TITAN trials (section 3.2.3.3 and 0) using the EQ-5D preference-based method, as recommended by NICE. [50] SPARTAN used the EQ-5D 3L as recommended in the NICE reference case, while TITAN used the EQ-5D 5L scale and then mapped values to the 3L scale using the crosswalk algorithm[51] as recommended by NICE.

For the SPARTAN trial, HRQoL measurements were taken for the pre-progression and post progression periods (until 12 months post-progression) as described in CS Table 63. The number of patients who had EQ-5D measured is shown in CS Figure 16. The CS states that rates of completion for the EQ-5D were more than 92% up to cycle 29 and more than 63% for the end of treatment visit and post-progression.

For the TITAN trial, HRQoL measurements were taken for the pre-progression and post progression periods (until 12 months post-progression) as described in CS Table 63. The number of patients who had EQ-5D measured is shown in CS Figure 29. The CS states that rates of completion for the EQ-5D ranged from 78% to 85% up to cycle 13 and 80% thereafter.

The company used regression models to estimate utilities for the nmHRPC and mHSPC health states from their clinical trial utility data. More details of the methods are described in CS Appendix R.

The utility values used for pre-progression and post-progression (1L mHRPC) are taken from the company trials. The company derived the utility values for 2L and 3L mHRPC by applying a relative decline ratio, estimated by dividing the 2L mHRPC utility by the 1L mHRPC utility from TA387. This ratio was then multiplied by the utility from the post-progression health state (1L mHRPC) from the company's trials. This process was repeated to estimate the 3L mHRPC utility. The utility values used in the company model are shown in Table 36 (CS Table 65).

Table 36 Summary of utility values for company base-case cost-effectiveness analysis

State	Indication	Mean
Pre-progression	nmHRPC	[redacted]
	mHSPC	[redacted]
Pre-progression (with AE/SRE)	nmHRPC	[redacted]
	mHSPC	[redacted]
1L mHRPC	nmHRPC	[redacted]
	mHSPC	[redacted]
2L mHRPC	nmHRPC	[redacted]
	mHSPC	[redacted]
3L mHRPC	nmHRPC	[redacted]
	mHSPC	[redacted]

Abbreviations: 1L: first line; 2L: second-line; 3L: third-line; ADT: androgen deprivation therapy; AE: adverse event; mHRPC: metastatic hormone-relapsed prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; SRE: skeletal-related event.

The problem with the company's approach is that it assumes that there will be a similar relative decline in utility for patients between health states in TA387 and the current appraisal. We find this unlikely as the trial had different starting populations and the effect of this appears to be underestimate utility values for 2L and 3L mHRPC. The ERG prefers to use the utility values from TA387 without any adjustment. The unadjusted utility values for

second-line and third-line mHRPC are shown in Table 37. We use these utility values in the ERG base case (section 6)

Table 37 ERG's preferred utility values for second-line and third-line treatment in mHRPC

Health state	Indication	Mean
2L mHRPC	nmHRPC	[redacted]
	mHSPC	[redacted]
3L mHRPC	nmHRPC	[redacted]
	mHSPC	[redacted]

4.2.10.3 Adverse event disutilities

In the company base case analysis, the adverse event disutilities were taken from EQ-5D values collected in the TITAN and SPARTAN trials as estimated using the regression analysis described in CS Appendix R. For each cycle, the utility decrement is calculated by multiplying the adverse event disutility with the incidence of adverse events and the proportions of patients in that health state. Scenario analyses are also conducted using literature values for the AE disutility values (CS Table 95 and 96).

In addition, a further utility decrement of 0.02 was applied for the first year for all patients receiving docetaxel (mHSPC only). This value was taken from the STAMPEDE trial and applied for one year, based on the assumption used in Woods et al.[32] For mHRPC health states, disutilities were estimated from the literature, based on relevant clinical trials for each subsequent treatment.

We consider that the adverse event disutility is overestimated for the mHSPC/nmHRPC health states as in the model when patients suffer an AE, a disutility for these patients is then applied for the remainder of that health state. However, Aes mostly only last for up to two weeks (CS Table 64). We have made this change for the adverse events in the ERG base case (section 6).

4.2.10.4 Age-related disutility

The company does not include age-related disutility in the model. The ERG notes that including age-adjusted utility is recommended by NICE DSU Technical Support Document 12. [52] Further we note that utility values for patients with nmHRPC have a lower utility value than the general population norm for the UK. Age-related disutility is unlikely to have a large impact on the model results as utility values are estimated for each treatment line and these

would have incorporated the age of patients. The ERG base case analysis therefore does not include an age-related disutility. We have included a scenario analysis that includes age-related disutility for the pre-progressed health state with utility values set to no more than the UK population norm (section 6).

ERG conclusion

The company's approach to estimating utility values is reasonable and consistent with the NICE reference case. The utility values for the mHSPC / nmHRPC / mHRPC 1st-line are taken from the company's TITAN and SPRTAN trials. The ERG has concerns on the estimation of the mHRPC second, and third line health state utility values and AE utilities and suggest alternative values.

4.2.11 Resources and costs

The economic model includes drug acquisition costs for the nmHRPC and mHSPC groups and subsequent treatments used on progression to mHRPC (first, second and third line), health state management costs, costs for managing adverse events and terminal care costs incurred at the end of life.

The company conducted a systematic literature review (SLR) to identify any relevant cost and healthcare resource use data associated with the treatment of patients with nmHRPC and mHSPC. The original searches were performed between 19th July 2018 and 13th August 2018. The final update was performed between 01 May 2020 and 04th June 2020.

Details of the search strategy and eligibility criteria are shown in CS Appendix I. The searches identified 16 relevant studies for nmHRPC. Of these, the most relevant is NICE TA580 for enzalutamide.[9] For mHSPC, the search identified 14 studies, with no studies from the UK.

The resource use in the company's model was largely based upon those used in the company submission for TA387 (Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated).[40]

4.2.11.1 Drug acquisition

The acquisition costs for each drug is taken from the Monthly Index of Medical Specialties (MIMS),[53] the UK drugs and pharmaceutical electronic market information tool (eMIT)[54] and from the British National Formulary (BNF).[55] Intended dosages were adjusted by the dose intensity observed in the trials for apalutamide and docetaxel.

Apalutamide is an oral treatment and is licensed at 4 x 60mg QD. The list price of apalutamide is £2,735 for 112 tablets (course of 28 days). Apalutamide is supplied to the NHS with a confidential patient access scheme (PAS) price discount.

The dosing, frequency and unit costs of the drugs are shown in Table 38 (CS Table 67). Docetaxel, cabazitaxel and radium-223 are given for a fixed duration whilst other treatments are given until disease progression (or intolerable side effects).

The company has reported all analyses using the list price of all subsequent treatments and the PAS price for apalutamide. The ERG replicated the company's analyses using the subsequent treatment PAS prices in a separate confidential appendix to this report.

Table 38 Dosing, frequency and unit costs per administration

Treatment		Drug acquisition costs			Dose / Frequency
		Cost per pack	Pack size	Unit	
Intervention and comparators	Apalutamide	£2,735.00 (list price)	112	Tablets	4 tabs / day
	Docetaxel	£20.96	1	Vial	Every 3 weeks
ADT individual therapies	Leuprorelin	£225.72	1	Syringe	Every 3 months
	Triptorelin	£207.00	1	Syringe	Every 3 months
	Goserelin	£70.00	1	Syringe	Every 28 days
	Bicalutamide	£1.74	28	Tablets	One per day
Subsequent therapies (if not included as a comparator)	Abiraterone	£2,735.00	56	Tablets	2 tabs / day
	Enzalutamide	£2,734.67	112	Tablets	4 tabs / day
	Cabazitaxel	£3,696.00	1	Vial	Every 3 weeks
	Radium-223	£4,040.00	1		Every 3 weeks
	BSC (prednisolone)	£0.28	28	Tablets	One per day

Abbreviations: ADT: androgen deprivation therapy; BSC: best supportive care.

Oral treatments are assumed to have no administration cost. ADT treatments are administered by syringe and require a nurse appointment and those administered by IV require a day case appointment (CS Table 68).

4.2.11.2 Subsequent treatment

The CS assumes that patients with mHRPC receive the same set of subsequent therapies after progressing from either nmHRPC or mHSPC. The proportion of patients receiving subsequent treatments is estimated from the company's mHSPC advisory board and is shown in CS Table 72. Scenario analyses were conducted by the company using alternative

market shares taken from the nmHRPC advisory board and the SPARTAN and TITAN trials (CS Table 95 and 96). However, it should be noted that many patients in the SPARTAN and TITAN trials had more than one novel therapy. The company provides an adjustment to the PFS2 and OS survival curves to remove the effect of patients having more than one novel therapy, as we have discussed earlier in section 4.2.6.2. The market shares for the nmHRPC advisory board and the SPARTAN and TITAN trials are shown in CS Appendix P.

Clinical advice to the ERG agrees that the estimated proportions of patients taking subsequent treatments in the company's model are reasonable. However, the ERG notes that patients with mHSPC treated with ADT alone also received docetaxel as a subsequent treatment. This is inappropriate for the company's analyses for people ineligible/unsuitable for docetaxel in mHSPC, as by definition, they are not able to receive docetaxel. Due to the low cost of docetaxel, this is unlikely to have a large impact on the model results.

The subsequent therapies consist of those administered continuously (abiraterone, enzalutamide and BSC) and those with a fixed duration (docetaxel, cabazitaxel and radium-223). The drug costs of continuous therapies are estimated by multiplying the per-cycle cost of each treatment by their market share and the number of patients in the relevant mHRPC health states. The costs of fixed therapies are estimated by multiplying the number of incident patients in first-line, second-line and third-line mHRPC by the market share and the total cost of the therapy. The number of vials administered for the fixed duration treatments are shown in CS Table 74.

The ERG notes an error in the calculation of third-line costs for fixed duration treatments for docetaxel + ADT (cells Q139 and,Q140) in the subs therapy costs worksheet. We correct this error in section 6.

The ERG notes an error in the estimation of incident patients for third-line mHRPC whereby the total number of incident patients for third-line mHRPC is greater than for second-line. This is clearly implausible and we correct it in section 6.

4.2.11.3 Time on treatment

Patients receive apalutamide plus ADT until disease progression or emergence of Aes. The time on treatment KM curves are shown in CS Figure 56 and 57 for the SPARTAN and TITAN trials respectively. The company fitted parametric curves to the time-on-treatment

data for apalutamide plus ADT. The CS notes that there is some crossover of the curves of predicted TTD and PFS. [redacted] The ERG agrees with the approach taken by the company and the curve chosen for TTD for apalutamide plus ADT.

For the ADT and the docetaxel plus ADT arms, the company assumes that all surviving patients will receive all treatments, i.e. TTD = PFS. A similar approach is taken for subsequent treatment lines of treatment. For subsequent treatments for mHRPC, the time on treatment is assumed to be equal to the time spent in the health states for first line, second-line and third-line.

4.2.11.4 Estimation of mean health state durations

The time spent in mHRPC on second-line and third-line treatments is estimated according to the mean health state durations from NICE TA387, shown in Table 39. The total time patients spend in the 2L and 3L mHRPC health states is determined by the area between the PFS2 and OS curves. Therefore, the mean health state durations are simply used to split patients between the 2L and 3L health states.

Constant probabilities were estimated to model the transition between health states by applying an exponential distribution to the mean time in health states. The durations from the abiraterone arm for TA387 are applied to the ADT alone and docetaxel plus ADT arms as the majority of patients in clinical practice are likely to receive an active first-line treatment for mHRPC. In a similar way, the durations from the ADT arm from TA387 are applied in the apalutamide plus ADT arm as these patients are not expected to receive a novel agent as a subsequent therapy.

Table 39 Mean health state durations in TA387

Health state	AAP	BSC
1L mHRPC	[redacted]	[redacted]
2L mHRPC	[redacted]	[redacted]
3L mHRPC	[redacted]	[redacted]
3L mHRPC (ERG estimate)	[redacted]	[redacted]
mHRPC LYs	[redacted]	[redacted]

The mean health state durations in TA387 are adjusted by multiplying by the mean post progression survival in the model and dividing by the mean life years in TA387 (see CS section B3.3.7.2). They are further adjusted by dividing by the proportion of patients who did not die in the pre-progression health state in the TITAN and SPARTAN. The ERG is unclear on the rationale for dividing by this value. We do not include this adjustment in the ERG base case in section 6.

The company provide more details on the mean health state durations in the response to clarification question B3 and the unredacted values of the mean health state durations in TA387 are shown in Table 20 of the clarification response. The ERG notes that there is some uncertainty over the mean health state durations for 2L and 3L mHRPC as the treatments differ for patients in TA387 to those in the current appraisal, particularly for estimates of the mean health state durations for the apalutamide plus ADT arm. Further we note that health state duration for 3L mHRPC is only for those on active treatment, whereas the majority of patients in 3L mHRPC are on best supportive care (CS Table 72). Therefore, we consider it is more appropriate to estimate the mean health state duration for 3L mHRPC by including those on BSC in TA387. The ERG's estimates for 3L mHRPC mean health state duration are shown in Table 39 and these are used in the ERG's base case, reported in section 6.

We note that there appears to be an error in cell 'PF_DOX!AJ9', see section 5.3.2 for more details. We correct this error in section 6.

4.2.11.5 Health state unit costs

Health state costs consisted of scheduled and unscheduled medical resource costs. Scheduled medical resource use and their frequency is shown in CS 77-79 for mHSPC, nmHRPC and mHRPC. The CS states that these were elicited from clinical experts at two advisory boards.

Clinical advice to the ERG suggests minor differences to the frequency of investigations as follows: for mHSPC, patients treated with apalutamide would receive PSA and other blood tests every 4 weeks for the first 3 months (rather than every 12 weeks) and then every 12 weeks thereafter. For nmHRPC patients treated with ADT would receive MRI scan every 26 weeks (rather than every 52 weeks).

Unplanned medical resource use (MRU) costs for all treatment for mHSPC, nmHRPC and mHRPC were assumed to be £21.57 per weekly cycle. The unplanned MRU costs were based upon NICE TA387.[56] The ERG asked for more clarification on the unplanned MRU costs (clarification question B13). The company stated that "It is unclear whether this cost captures all unscheduled resource use including or excluding the treatment of adverse events and therefore whether there is any risk of double counting" (Clarification question B13, p45)". The company provided a scenario where unscheduled resource use costs were omitted and they stated that omitting these costs had a minimal effect on model results. As unscheduled MRU costs should be counted for by the adverse event management costs, we have omitted unscheduled resource costs in the ERG base case analysis (section 6).

Health state unit costs are not reported in the CS but are shown in the economic model (Resource use costs worksheet). These were taken from 2018/2019 NHS reference costs[57] and 2019 PSSRU costs.[58] The health state costs for each of the treatments are shown in CS Table 80.

4.2.11.6 Cost of terminal care

The company's model includes a cost of end-of-life care of £15,786 taken from Round et al[59]). The reported cost in that study was inflated to 2018/19 prices using the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care.[58]

4.2.11.7 Adverse event costs

The model includes the costs of managing grade 3+ adverse events, shown in CS Table 81. These AE costs were taken from TA387[56] and inflated to 2018/19 costs using the PSSRU inflation indices. The ERG notes that the values used in the model differ from those presented in CS Table 81 and appear to have been inflated twice. In addition, the inflation indices used by the company are for prices only whereas the ERG prefers to use the prices and pay inflation indices. In response to clarification question B14, the company acknowledged that inflation had been applied twice in error. They provided a scenario with corrected values and stated that these changes had a minor impact on the model results.

The cost of managing neutropenia in CS Table 81 is £862.79. We consider this an overestimate as patients with neutropenia would not be hospitalised and would only require an additional outpatient visit and blood test (£150.16). The ERG has changed the costs of managing this adverse event in section 6.

The cost of all AEs for each comparator in the model is calculated by estimating a weighted average of the probability of experiencing each event from the relevant trial data, multiplied

by the cost of each event. The cost per cycle is calculated by dividing the total incidence from each study by the median follow-up. Adverse events are applied each model cycle for all patients remaining on treatment.

We consider that the costs of adverse events for docetaxel treatment have been overestimated for mHSPC. Docetaxel is given for six cycles and the majority of the costs of managing side effects would be during this 18-week period. We therefore consider that AE costs should only be costed up to the trial follow-up duration (26 weeks). The ERG changes the costs of adverse events for docetaxel in section 6. The CS states that real world data on the usage of docetaxel suggest higher rates of grade ≥3 neutropenia and febrile neutropenia of 36.3% and 18.2%.[60] The ERG includes these estimates of Aes in a scenario analysis in section 6.

ERG conclusion

The approach taken by the company for estimating costs and resource use are reasonable and appropriate and consistent with previous technology appraisals for prostate cancer. The ERG has identified errors in the calculation of adverse events costs and subsequent therapy costs and suggest minor changes to the cost outpatient visits, the cost of managing neutropenia and health state resource use.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

5.1.1 nmHRPC

CS Section B.3.7.1 reports the base case results for apalutamide plus ADT versus ADT alone for the nmHRPC indication. The results show that apalutamide plus ADT offers [redacted] of [redacted] and a mean QALY gain of [redacted] compared with ADT alone (Table 40). Apalutamide plus ADT therefore dominates ADT alone, i.e. it is cheaper and more effective. Disaggregated results by health state are shown in CS Table 87.

Table 40 Company's base case results for nmHRPC (discounted, PAS price for apalutamide)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£/QALY)
ADT alone	[redacted]	5.03	[redacted]				
Apalutamide plus ADT	[redacted]	5.70	[redacted]	[redacted]	0.67	[redacted]	Dominates
Source: reproduced from CS Table 85.							

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£/QALY)
ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gain; QALYs: quality-adjusted life years.							

5.1.2 mHSPC

CS Section B.3.7.2 reports the base case results for apalutamide plus ADT versus ADT alone and docetaxel plus ADT for the mHSPC indication. The results show that apalutamide plus ADT offers a mean QALY gain of [redacted] for an additional mean cost of [redacted], giving an ICER of £38,983 per QALY compared with docetaxel plus ADT (Table 41). In the subgroup of patients ineligible to receive docetaxel, apalutamide plus ADT provides an ICER of £25,329 compared with ADT alone (Table 41). Disaggregated results by health state are shown in CS Table 87.

Table 41 Company's base case fully incremental results for mHSPC (discounted, PAS price for apalutamide)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£/QALY)	ICER (£/QALY): APA vs. ADT
ADT alone	[redacted]	4.588	[redacted]					
Docetaxel plus ADT	[redacted]	5.501	[redacted]	[redacted]	0.913	[redacted]	9,633	
Apalutamide plus ADT	[redacted]	6.023	[redacted]	[redacted]	0.523	[redacted]	38,983	25,329
Source: reproduced from CS Table 88 and CS Table 89. ADT: androgen deprivation therapy; APA: apalutamide plus ADT; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gain; QALYs: quality-adjusted life years.								

The cost-effectiveness results presented include a confidential PAS discount price for apalutamide but do not include existing PAS discounts for the subsequent therapies. Therefore, the ICERs do not reflect actual prices that would be paid by the NHS. The results including all agreed PAS discounts for subsequent therapies as well as the company's proposed price discount for apalutamide are presented in a separate confidential addendum to this ERG report.

5.2 Company's sensitivity analyses

5.2.1 Deterministic sensitivity analyses

The company lists the parameters included in the deterministic sensitivity analyses in CS Appendix P. The upper and lower bounds of the parameters were varied as (i) ± 1.96 *

standard error (SE) of the base case value (or mean), (ii) within ± 10% of the base case value when SE is unknown, (iii) and for discount rate, the variation advised by NICE (0% and 6%).

Results of the deterministic sensitivity analyses are presented as net monetary benefit at a willingness to pay of £30,000 per QALY since the ICER is negative for some of them. CS Figures 63, 64 and 65 present tornado diagrams for nmHRPC (apalutamide plus ADT versus ADT alone), mHSPC (apalutamide plus ADT versus ADT alone) and mHSPC (apalutamide plus ADT versus docetaxel plus ADT), respectively. The diagrams show that the urologist/oncologist unit cost, second line health state utility value and unplanned resource use annual costs are the key drivers of the model results for the nmHRPC indication. For the mHSPC indication, unplanned resource use annual costs, subsequent treatment durations and mean health state durations are the key drivers of the model results when comparing apalutamide plus ADT versus ADT alone. For the comparison against docetaxel plus ADT, the PFS2 and OS HR have the most significant impact on the results.

The ERG notes that clinical effectiveness parameters (namely, the parameters related with PFS, PFS2 and OS parametric curves) were not varied in these analyses. Additionally, we note that the deterministic sensitivity analysis does not include the variation of the discount rate because there is an error in the model. The active cells for discount rate in the 'Parameters' sheet that are being used for the deterministic sensitivity analysis are not the same active cells that are being used to calculate discounted results in the model. This error and the suggested correction are listed in 5.3.2**Error! Reference source not found.**. Figure 23 shows the corrected net monetary benefit results of the deterministic sensitivity analyses for nmHRPC.

The ERG considers that, where possible, results should be presented as ICERs because it enables a more intuitive interpretation. In the case of the mHSPC, the ICER is negative for only one scenario, therefore the results of the deterministic sensitivity analyses for this indication, with the discount rate error amended, are presented as ICERs in Figure 24 and Figure 25. For both nmHRPC and mHSPC indications, the discount rate is the parameter which has most impact on the model results, with the exception of the HR for the comparison against docetaxel plus ADT.

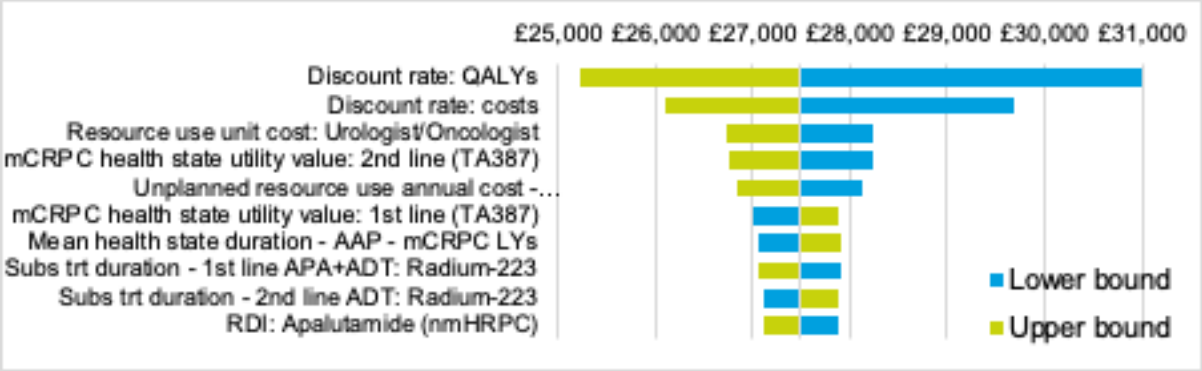


Figure 23 Net Monetary Benefit results of deterministic sensitivity analyses for nmHRPC: apalutamide plus ADT versus ADT alone (ERG analysis with discount rate correction)

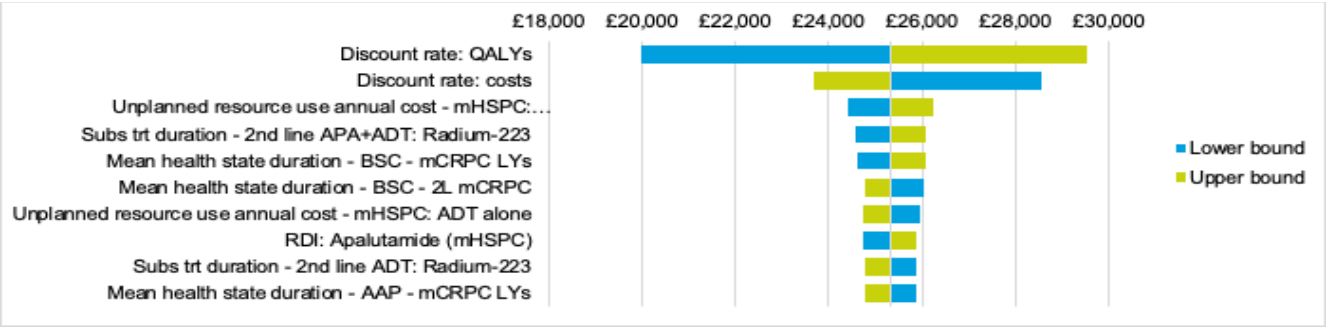


Figure 24 ICER results of deterministic sensitivity analyses for mHSPC: apalutamide plus ADT versus ADT alone (ERG analysis with discount rate correction)

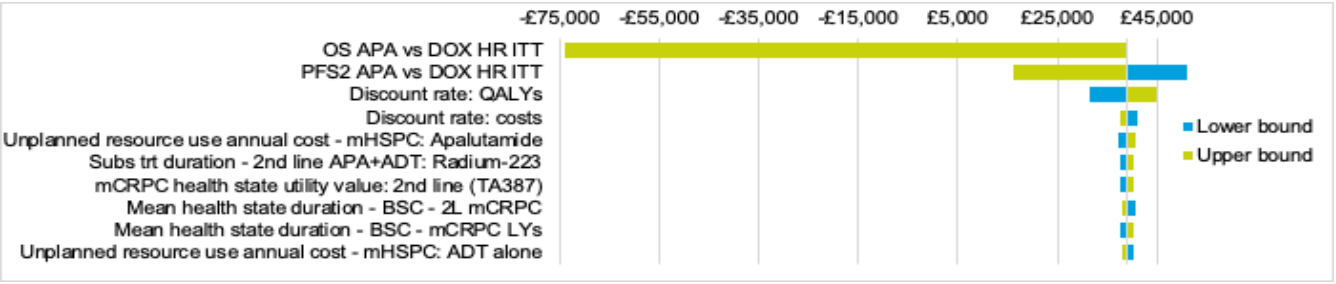


Figure 25 ICER results of deterministic sensitivity analyses for mHSPC: apalutamide plus ADT versus docetaxel plus ADT (ERG analysis with discount rate correction)

CS Table 95 reports the results of the scenario analyses for nmHRPC and CS Tables 96 and 97 report the results for mHSPC.

Most of the scenario analyses do not have a significant impact on the model results, with the exception of survival curve selections for PFS, the method for the transition of patients between first and second line mHRPC health states and the subsequent therapy market shares. The company states that using alternative extrapolation curves for PFS results in the PFS and PFS2 curves crossing, which is implausible. They also state that the use of PFS2

instead of mean health state durations is more appropriate to split patients between first and second line mHRPC since PFS2 is an endpoint from the trials that inform most of the clinical parameters of this appraisal (SPARTAN and TITAN) and mean health state durations come from an external study with a slightly different population and characteristics. Regarding the alternative subsequent therapy market shares, the company argues that the market shares from SPARTAN and TITAN trials are not relevant "as they do not align with the NHS England one novel therapy commissioning policy" (CS page 248).

We extend the range of scenario analyses to include alternative survival extrapolation approaches, alternative utility values, alternative treatment waning start and end points and inclusion of age-related disutility (see section 6)

5.2.2 Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis to assess parameter uncertainty. They assigned a normal distribution for mean health state durations, subsequent treatment durations, adverse event durations, median trial follow-ups, drug dosages and costs; and the beta distribution for relative dose intensity, docetaxel completion rates, ADT market shares, adverse event incidences, mHRPC utilities and adverse event disutilities. The ERG notes that the gamma distribution is the most standard distribution for costs but was not used in this model. A multinormal distribution was assigned to the nmHRPC and mHSPC pre-progression utilities but it remains unclear whether and how these utilities were included in the probabilistic sensitivity analysis. CS Tables 93 and 94 summarise the probabilistic results for nmHRPC and mHSPC, respectively; CS Figures 58, 59 and 60 present the cost-effectiveness planes; and CS Figures 61 and 62 present the cost-effectiveness acceptability curves (CEAC). The probabilistic results are consistent with the deterministic results, as stated in the CS. At a willingness-to-pay threshold of £30,000 per QALY, apalutamide plus ADT has a 100% probability of being cost-effective compared to ADT alone for nmHRPC; and 31.1% probability compared to ADT alone and docetaxel plus ADT for mHSPC.

5.3 Model validation and face validity check

The company describes their approach to model validation in CS section B.3.9. Expert opinion, from four clinical experts and three health economists for nmHRPC and five clinical experts and three health economists for mHSPC, validated the model inputs and assumptions listed in CS section B.3.9.2.

The model was validated by an independent modeller who (1) checked all formulae and labelling in the model and (2) changed each model parameter to a sensible upper and lower bound and checked the resulting outcomes against the expected ones. More details can be found in CS section B.3.9.3.

Post-progression survival was compared against estimates from previous NICE appraisals for mHRPC (TA387 TA377 TA259]). The mean post-progression survival from the model was calculated by dividing the mean life years spent in mHRPC health states by the proportion of patients who progress. The proportion of patients who progress was estimated by dividing the number of MFS/rPFS events that were deaths reported in the SPARTAN and TITAN trials by the total number of deaths in these studies. CS Table 98 reports the predicted post-progression survival for the current model and for the previous appraisals. The post-progression survivals estimated from the model are not widely different from the TA387 and TA377 estimates. However, they are significantly different from the TA259 estimates, which are much lower than the others. The company argues that this is expected "since this submission focussed on later stages of mHRPC, following prior cytotoxic therapy, where patients would have poorer survival rates" (CS page 254).

The ERG considers that comparing the life-years spent in the mHRPC health states of the model directly against the previous NICE appraisals' post-progression survival results would be more reasonable than adjusting the model life-years for the proportion of patients who progress. Therefore, we update CS Table 98, without the adjustment, as part of the ERG's model validation (see Table 45).

Overall survival estimates of ADT alone for both indications were also compared against long-term survival data from the literature (the same studies used to inform the 'informed fits' analysis). CS Figure 66 shows the OS KM curves from the literature and CS Table 99 summarizes the percentage of patients alive at given timepoints (1, 2, 3, 5, 7 and 9 years) based upon the OS estimated from the model and from the literature. OS historical data are consistent with modelled OS for mHSPC. The company claims that these cross-validity checks are not as relevant for nmHRPC as the SPARTAN trial has a longer follow-up than the studies in the literature.

ERG conclusions

The company conducted face validity checks, a comprehensive model functionality validation as well as cross validity checks and external validation, comparing the model results with previous NICE appraisals and long-term data from literature.

However, they did not report that they had conducted any internal validity checks, i.e., comparing the model results with the trial data. Moreover, we believe that they did not use the best approach to compare post progression survival estimates and we adopted a different one in the ERG's model validation below.

5.3.1.1 ERG model validation

The ERG checked the economic model for transparency and validity. We conducted a range of tests to verify model inputs, calculations and outputs:

- Cross-checking all parameter inputs against values reported in the CS and cited sources;
- Checking the individual equations within the model;
- A range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed;
- Checking all model outputs against results cited in the CS, including the base case, probabilistic sensitivity analyses, deterministic sensitivity analyses and manually-run scenarios.

The model is generally well-implemented, with some minor errors in parameter inputs and coding. The company provided an updated model with their clarification response, in which some original issues were corrected – KM data for ADT in nmHRPC, rates of adverse events and adverse event unit costs. Nevertheless, the ERG found other errors, listed in Appendix 9.5.

5.3.1.2 Cross-validity checks

As explained above, we compared the modelled life-years spent in mHRPC health states with the previous NICE appraisals post-progression survival for mHRPC TA387, TA377, and TA259 (Table 42). The modelled outcomes reported below come from the company's updated model provided with their clarification response. The mean life years spent in the post progression health states of the current model are generally consistent with the post progression survival from the previous NICE appraisals. The post progression survival of ADT alone for mHSPC are lower than all the previous NICE appraisals' estimates and the post progression survival of docetaxel plus ADT for mHSPC are lower than the TA387 and TA377 estimates. We note that changes in the post progression health state durations were explored by the company in their deterministic and probabilistic sensitivity analysis and were among the main key drivers of the model results for both indications (Figure 23, Figure 24 and Figure 25).

Table 42 Comparison of modelled post progression survival against previous NICE appraisals for mHRPC

Source (time horizon)	Indication	Treatment	Post progression survival (years)	
			1L+2L+3L [a]	2L+3L [b]
Current appraisal (32 years)	nmHRPC	Apalutamide plus ADT	2.51	0.71
		ADT alone	3.46	1.42
	mHSPC	Apalutamide plus ADT	2.55	1.51
		ADT alone	2.29	1.05
		Docetaxel plus ADT	2.79	1.83
TA387 (until 100 years of age)	mHRPC	Abiraterone acetate	3.34	-
		BSC	2.72	-
TA377 (10 years)	mHRPC	Enzalutamide	3.06	-
		Abiraterone acetate	2.86	-
		BSC	2.61	-
TA259 (10 years)	mHRPC (2L)	Abiraterone acetate	-	1.75
		PP	-	1.385
		MP	-	1.385

[a] The life-years spent in first, second and third line health states.
[b] The life-years spent in second and third line health states.
1L: first line; 2L: second line; 3L: third line; ADT: androgen deprivation therapy, BSC: best supportive care; LYs: life years; mHRPC: metastatic hormone resistant prostate cancer; mHSPC: metastatic hormone sensitive prostate cancer, MP: mitoxantrone plus prednisolone; nmHRPC: non-metastatic hormone resistant prostate cancer; PP: prednisolone plus placebo.

We also compared the modelled OS estimates for docetaxel from the current appraisal with a previous study performed in the UK for patients with mHSPC in the STAMPEDE trial.[61] We note that the OS estimates from the current appraisal are consistent with the STAMPEDE estimates (Table 43).

Table 43 Comparison of the modelled OS estimates with STAMPEDE OS estimates for docetaxel in mHSPC

Treatment	Data	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 9
OS								
Docetaxel plus ADT	Modelled data	0.924	0.810	0.688	0.573	0.466	0.372	0.173
	STAMPEDE data	0.930	0.780	0.680	0.580	0.500	0.420	0.210

ADT: androgen deprivation therapy, mHSPC: metastatic hormone sensitive prostate cancer, OS: overall survival.

5.3.1.3 Internal validity checks

We compared the company's modelled estimates with the observed clinical data. We summarise these results for nmHRPC in Table 44 and for mHSPC in Table 45. The

modelled and observed data reported below come from the company's updated model provided with their clarification response. The estimates for PFS, PFS2 and OS from the observed data and the model are generally comparable for both treatment arms and both indications.

Table 44 Comparison of the modelled estimates with the observed clinical data for nmHRPC

Treatment	Data	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
PFS							
Apalutamide plus ADT	Observed data	0.859	0.682	0.514	-	-	-
	Modelled data	0.879	0.675	0.468	-	-	-
ADT alone	Observed data	0.579	0.296	0.165	-	-	-
	Modelled data	0.617	0.295	0.120	-	-	-
PFS2							
Apalutamide plus ADT	Observed data [a]	0.962	0.839	0.699	0.583	0.464	0.454
	Modelled data	0.953	0.853	0.720	0.579	0.445	0.326
ADT alone	Observed data [a]	0.931	0.766	0.557	0.377	0.231	-
	Modelled data	0.921	0.756	0.558	0.378	0.235	-
OS							
Apalutamide plus ADT	Observed data [a]	0.978	0.907	0.810	0.677	0.550	0.415
	Modelled data	0.969	0.903	0.802	0.679	0.549	0.423
ADT alone	Observed data [a]	0.974	0.898	0.755	0.597	0.485	0.447
	Modelled data	0.964	0.881	0.755	0.610	0.463	0.331

[a] Novel agent adjusted
ADT: androgen deprivation therapy, nmHRPC: non-metastatic hormone refractory prostate cancer, OS: overall survival, PFS: progression-free survival, PFS2: secondary progression-free survival

Table 45 Comparison of the modelled estimates with the observed clinical data for mHSPC

Treatment	Data	Year 0.5	Year 1	Year 1.5	Year 2	Year 2.5
PFS						
Apalutamide plus ADT	Observed data	0.953	0.844	0.789	0.689	0.626
	Modelled data	0.948	0.865	0.772	0.676	0.584
ADT alone	Observed data	0.871	0.703	0.592	0.483	0.461
	Modelled data	0.868	0.719	0.582	0.463	0.364
PFS2						
Apalutamide plus ADT	Observed data	0.981	0.942	0.870	0.813	0.765
	Modelled data	0.974	0.932	0.876	0.810	0.738

Treatment	Data	Year 0.5	Year 1	Year 1.5	Year 2	Year 2.5
ADT alone	Observed data	0.971	0.901	0.816	0.728	0.697
	Modelled data	0.963	0.901	0.821	0.730	0.634
OS						
Apalutamide plus ADT	Observed data	0.985	0.946	0.883	0.825	0.771
	Modelled data	0.974	0.933	0.885	0.832	0.777
ADT alone	Observed data	0.973	0.923	0.848	0.737	0.706
	Modelled data	0.963	0.903	0.835	0.764	0.691
ADT: androgen deprivation therapy, nmHRPC: non-metastatic hormone refractory prostate cancer, OS: overall survival, PFS: progression-free survival, PFS2: secondary progression-free survival						

5.3.2 ERG corrections to the company's model

As previously stated, the company's model was generally well-implemented, with no substantive errors. However, there are some minor errors that we identified. In addition, the ERG notes that the incidence of patients in the third line mHRPC health state is incorrectly modelled, because the incidence of patients in the third line is higher than the incidence of patients in second line, which is not clinically plausible. Therefore, a correction has been made in the ERG base case. Appendix 9.5 – Table A lists the errors that the ERG considers should be amended as they have some impact on the model results. The remaining issues, which do not affect the model results, are presented in Appendix 9.5 – Table B.

The ERG re-ran the analyses with the corrected formulas. These changes, added to the company's corrections, maintain the dominance of apalutamide plus ADT versus ADT alone for nmHRPC (Table 46) and lead to a decrease in the base case ICER from £38,983 (company's base case) to £34,636 per QALY for the comparison against docetaxel, and from £25,329 to £25,002 per QALY against ADT alone, for mHSPC (Table 47).

Table 46 Cost-effectiveness results from ERG corrections for nmHRPC (discounted, PAS price for apalutamide)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£/QALY)
ADT alone	[redacted]	5.03	[redacted]				
Apalutamide plus ADT	[redacted]	5.70	[redacted]	[redacted]	0.67	[redacted]	Dominates
ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gain; QALYs: quality-adjusted life years.							

Table 47 Cost-effectiveness results from ERG corrections for mHSPC (discounted, PAS price for apalutamide)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£/QALY)	ICER (£/ QALY): APA vs. ADT
ADT alone	[redacted]	4.59	[redacted]					
Docetaxel plus ADT	[redacted]	5.50	[redacted]	[redacted]	0.91	[redacted]	14,102	
Apalutamide plus ADT	[redacted]	6.02	[redacted]	[redacted]	0.52	[redacted]	34,636	25,002
ADT: androgen deprivation therapy; APA: apalutamide plus ADT; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gain; QALYs: quality-adjusted life years.								

We re-ran the company's scenario analysis (summarised in CS Tables 95, 96 and 97) with the ERG corrected model. The results are presented in Table 48 for nmHRPC and in Table 49 for mHSPC. These results show that, in general, the ICERs decrease slightly (no more than £6,000 per QALY) in comparison to the results from the company's scenarios.

Table 48 Results of the company's scenario analysis using the ERG corrected model for nmHRPC (discounted, PAS price for apalutamide)

Scenario	ICER (£/QALY)
Base case (ERG corrected)	Dominates
Time horizon: 30 years	Dominates
Time horizon: 20 years	Dominates
Time horizon: 10 years	Dominates
Unadjusted SPARTAN data for one novel therapy rule	Dominates
MFS extrapolation: Log-logistic	£3,007
MFS extrapolation: Log-normal	£3,151
PFS2 extrapolation: Log-logistic	Dominates
PFS2 extrapolation: Log-normal	Dominates
PFS2 extrapolation: Generalized gamma	Dominates
OS extrapolation: Generalized gamma	Dominates
Mean health state durations from TA387 for 1L mHRPC	Dominates
Treatment waning between 10-15 years	Dominates
Subsequent therapy market shares: SPARTAN trial	£31,543
Subsequent therapy market shares: nmHRPC advisory board	Dominates
AE disutilities: literature values	Dominates
mHRPC utilities: assumed constant through mHRPC	Dominates
1L: first line; ADT: androgen deprivation therapy; AE: adverse event; APA: apalutamide plus ADT; ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; MFS: metastatic-free survival; mHSPC: metastatic hormone sensitive prostate cancer; mHRPC: metastatic hormone resistant prostate cancer; nmHRPC: non metastatic hormone resistant prostate cancer; OS: overall survival; PFS2: secondary progression-free survival; QALYs: quality-adjusted life years.	

Table 49 Results of the company's scenario analysis using the ERG corrected model for mHSPC, versus ADT alone (discounted, PAS price for apalutamide)

Scenario	ICER (£/QALY) vs. ADT alone	ICER (£/QALY) vs. DOX
Base case (ERG corrected)	£25,002	£34,636
Time horizon: 30 years	£25,002	£34,636
Time horizon: 20 years	£25,042	£34,792
Time horizon: 10 years	£27,185	£40,441
rPFS extrapolation: Exponential	£38,317	£63,111
rPFS extrapolation: Log-logistic	£37,370	£55,837
rPFS extrapolation: Log-normal	£39,609	£61,906
OS extrapolation: Log-logistic	£23,712	£27,651
OS extrapolation: Log-normal	£21,688	£22,110
OS extrapolation: Generalized gamma	£23,267	£29,350
OS extrapolation: Gompertz	£27,834	£36,673
OS curve fitting approach: Unstratified curves	£29,178	£45,199
Mean health state durations from TA387 for 1L mHRPC	£27,573	£3,104
Treatment waning between 10-15 years	£25,630	£35,822
Subsequent therapy market shares: TITAN trial	£58,111	£82,864
Subsequent therapy market shares: nmHRPC advisory board	£16,987	£27,401
Utility source: STAMPEDE	£25,094	£33,563
AE disutilities: literature values	£24,168	£35,131
mHRPC utilities: assumed constant throughout mHRPC	£22,868	£38,634

1L: first line; ADT: androgen deprivation therapy; AE: adverse event; APA: apalutamide plus ADT; DOX: docetaxel plus ADT; ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; mHSPC: metastatic hormone sensitive prostate cancer; mHRPC: metastatic hormone resistant prostate cancer; nmHRPC: non metastatic hormone resistant prostate cancer; OS: overall survival; QALYs: quality-adjusted life years, rPFS: radiographic progression-free survival.

5.3.3 ERG summary of key issues and additional analyses

A full summary of ERG observations on key aspects of the company's economic model is presented in Table 50.

Table 50 ERG observations of the key aspects of the company's economic model

Parameter	Company base case	ERG comment	ERG base case
Survival curves – nmHRPC			
MFS	Independently modelled using Weibull distributions (for both arms) fitted to data unadjusted for crossover.	We agree with the company's assumption.	Independently modelled using Weibull distributions (for both arms) fitted to data unadjusted for crossover.
PFS2	Jointly modelled with Weibull distributions fitted to data adjusted for the novel therapy restriction and crossover without re-censoring, satisfying criteria listed in Table 28.	We agree with the company's assumption. Nevertheless, both analyses with and without re-censoring are recommended for treatment switching. RPFSTM with re-censoring has been shown to be more biased. It is not clear, however, whether this is relevant to the 'modified' RPFSTM.	Jointly modelled with Weibull distributions fitted to data adjusted for the novel therapy restriction and crossover without re-censoring.
OS	Jointly modelled with Weibull distributions fitted to data adjusted for novel therapy restriction and crossover without re-censoring.	Based on expert's advice, the Weibull model for ADT underestimates survival at 10 and 15 years, while the generalised gamma model better predicts long-term survival. The generalised gamma curves for both arms have a good visual fit to the Kaplan-Meier estimates from SPARTAN, and have lower AIC and BIC scores compared to those for the Weibull models.	Jointly modelled using generalised gamma distributions (for both arms) fitted to data adjusted for novel therapy restriction and crossover without re-censoring.
Survival curves – nmHRPC			
rPFS	Independently modelled with Weibull distributions fitted to data unadjusted for novel therapy restriction.	We agree with the company's assumption.	Independently modelled with Weibull distributions fitted to data unadjusted for novel therapy restriction.
PFS2	Jointly modelled with Weibull distributions fitted to data unadjusted for novel therapy restriction.	We agree with the company's assumption.	Jointly modelled with Weibull distributions fitted to data unadjusted for novel therapy restriction.

OS	Independently modelled with Weibull distributions based on 'informed fits' approach, not adjusted for novel therapy restriction.	We agree with the company's assumption.	Independently modelled with Weibull distributions based on 'informed fits' approach, not adjusted for novel therapy restriction.
Treatment waning	Not included in the base case	Literature suggests that resistance to novel therapies, such as enzalutamide and abiraterone, is likely to develop with time, but relevant long-term clinical evidence is not available. This has been confirmed by our clinical expert. Therefore, we explore potential impact of treatment waning in scenario(s) only.	Not included in the base case
Duration of health states (2L and 3L mHRPC)	The duration for health states used in the model use the durations from TA387, applied to the total duration in post progression in the model. This is adjusted by dividing by the proportion of patients who did not die in the pre-progression health state in the TITAN and SPARTAN.	The ERG is unclear on the rationale of dividing by this value, which appears counterintuitive.	We do not include this adjustment in the ERG base case in section 6.
3L mHRPC	Mean health state duration for 3L mHRPC only includes active treatment.	3L mHRPC health state duration includes time spent with active treatment and BSC.	Should also include time spent in BSC. 3L mHRPC: AAP [redacted]; ADT [redacted].
Utility	Company base case model estimates: nmHRPC: Pre-progression: 0.8233 1L mHRPC: 0.7713 2L mHRPC: 0.5808 3L mHRPC: 0.4626 mHSPC: Pre-progression: 0.8047 1L mHRPC: 0.6981 2L mHRPC: 0.5257 3L mHRPC: 0.4206	The ERG considers a better approach is to use unadjusted utility values from TA387 for the second-line and third-line mHRPC utilities.	ERG base case model estimates: nmHRPC Pre-progression: 0.8233 1L mHRPC: 0.7713 2L mHRPC: **0.625** 3L mHRPC: **0.50** mHSPC: Pre-progression: 0.8047 1L mHRPC: 0.6981 2L mHRPC: **0.625** 3L mHRPC: **0.50**

AE disutility	When patients suffer an AE, a disutility for these patients is then applied for the remainder of that health state.	Disutility should be only applied for a short period for patients with Aes.	Disutility applied for 2 weeks for patients with Aes.
Health state costs	Unscheduled health state costs are included.	As unscheduled MRU costs should be counted for by the adverse event management costs, the ERG have omitted unscheduled resource costs	Unscheduled health state costs are omitted.
AE costs	AE costs for docetaxel are applied for the whole duration of pre-progression.	Docetaxel is given for six cycles and the majority of side effects would be during this 18-week period.	AE costs for docetaxel are applied for first ½ years of pre-progression.
	The cost of managing neutropenia in CS Table 81 is £862.79.	We consider this an overestimate as patients with neutropenia would not be hospitalised and would only require an additional outpatient visit and blood test	The cost of managing neutropenia is £150.16.
Resource use	Resource use shown in Table CS Table 77, 78 and 79.	Some changes to resource use suggested by our clinical experts.	Resource use shown in Appendix 9.6.
1L: first line; 2L: second line; 3L: third line; ADT: androgen deprivation therapy; AE: adverse event; BSC: best supportive care; ERG: evidence review group; MFS: metastasis-free survival; mHRPC: metastatic hormone relapsed prostate cancer; mHSPC: metastatic hormone sensitive prostate cancer; MRU: medical resource use; nmHRPC: non metastatic hormone relapsed prostate cancer; PFS": secondary progression free survival; OS: overall survival; rPFS: radiographic progression free survival; RPFSTM: Rank Preserving Structural Failure Time Model.			

6 ERG'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

Based on the ERG critique of the company's model assumptions (as described in Table 50), we performed a range of additional scenario analyses (presented in Table 51 and Table 52) on the following model assumptions:

- Use KM data for MFS until week 120 and extrapolated tail thereafter (in nmHRPC) (see section 4.2.7.1);
- Use independently fitted curves with log-logistic, log-normal and generalised gamma to extrapolate PFS2 for nmHRPC;
- Use jointly and independently fitted curves with generalised gamma to extrapolate OS for nmHRPC;

- The mean health state durations of first, second and third line mHRPC health states were not adjusted for the proportion of patients not dying in the pre-progression state;
- The mean health state duration of third line mHRPC health state includes both the time spent in active treatment and BSC from TA387;
- Varying the treatment waning start and end points;
- The health state utilities for second and third line mHRPC health states were not adjusted for the first line mHRPC utility value;
- The duration of AE disutilities in the pre progression health state is two weeks;
- Include age-related disutility for pre-progression health state
- The duration of AE costs for docetaxel is 6 months;
- The neutropenia cost does not include hospitalization (=£150.16);
- The resource use for nmHRPC and mHSPC is based on the ERG's clinical advice; and
- The unscheduled MRU costs were excluded.

The scenario analyses were performed on the ERG's corrected company model. We note:
For nmHRPC:

- Apalutamide plus ADT dominates ADT alone in all the scenarios tested for nmHRPC, i.e. it is cheaper and more effective.

For mHSPC:

- The ICERs range from £22,709 per QALY (scenario: second and third line mHRPC health states utility values from TA580) to £28,516 per QALY (scenario: PFS2 extrapolated as jointly fitted curves with Gompertz) for apalutamide plus ADT compared to ADT alone.
- For the comparison against docetaxel plus ADT, the ICERs range from £33,569 per QALY (scenario: unscheduled MRU costs excluded) to £43,475 per QALY (scenario: second and third line mHRPC health states utility values from TA580).
- Assuming jointly fitted curves with Gompertz to extrapolate PFS2 and a treatment waning between 5 and 10 years had the greatest impact on the cost-effectiveness results versus ADT alone; the ICER increased to £28,516 per QALY and £27,947 per QALY, respectively.
- Assuming TA580 as the source for second and third line mHRPC health states utility values and a duration of adverse event costs for docetaxel of 6 months had the greatest impact on the cost-effectiveness results versus docetaxel plus ADT; the ICER increased to £43,475 per QALY and £42,272 per QALY, respectively.
- The remaining scenarios did not change the ICER more than £5,000 per QALY.

Table 51 Additional analyses conducted by the ERG on the company's base case for nmHRPC (ERG corrected, discounted, PAS price for apalutamide)

Scenario	Treatment	Total costs	Total QALYs	ICER (£/QALY)
Corrected company base case	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
MFS extrapolation: use KM data and extrapolated tail	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
PFS2 extrapolation: independently fitted log-logistic	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
PFS2 extrapolation: independently fitted log-normal	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
PFS2 extrapolation: independently fitted generalised gamma	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
OS extrapolation: jointly fitted generalised gamma	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
OS extrapolation: independently fitted generalised gamma	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
Unadjusted duration of mHRPC health states	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
Mean health state duration for 3L based on the active treatment and BSC durations from TA387	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
Treatment waning: 5-10 years	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
Unadjusted health state utilities for 2L/3L mHRPC	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
2L/3L mHRPC utility values from TA580	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
2L/3L mHRPC utility values from TA377	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
Duration of AE disutilies in the pre progression health state – 2 weeks	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
Include age-related disutility	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
Neutropenia cost – £150.16	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
Resource use based on the ERG's clinical advice	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
Exclude unscheduled MRU costs	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates

2L: second line, 3L: third line; ADT: androgen deprivation therapy; AE: adverse event; APA: apalutamide; BSC: best supportive care; ERG: evidence review group; ICER: incremental cost-effectiveness ratio; KM: Kaplan-Meier; MFS: metastasis-free survival; mHRPC: metastatic hormone relapsed prostate cancer; MRU: medical resource use; OS: overall survival; PFS2: secondary progression free survival; QALY: quality-adjusted life-years.

Table 52 Additional analyses conducted by the ERG on the company's base case for mHSPC (ERG corrected, discounted, PAS price for apalutamide)

Scenario	Treatment	Total costs	Total QALYs	ICER (£/QALY)	
				APA vs. DOX	APA vs. ADT alone

Corrected company base case	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£34,636	£25,002
PFS2 extrapolation: jointly fitted Gompertz	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£38,993	£28,516
Unadjusted duration of mHRPC health states	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£34,665	£25,009
Mean health state duration for 3L based on the active treatment and BSC durations from TA387	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£38,172	£25,936
Treatment waning: 5-10 years	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£39,531	£27,947
Unadjusted health state utilities for 2L/3L	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£37,544	£24,231
2L/3L mHRPC utility values from TA580	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£43,475	£22,709
2L/3L mHRPC utility values from TA377	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£37,819	£23,460
Duration of AE disutilities in the pre progression health state – 2 weeks	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	35,500	£24,139
Include age-related disutility	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£36,246	£25,842
Duration of AE costs for docetaxel – 6 months	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£42,272	£25,002
Neutropenia cost – £150.16	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£38,508	£24,777
Resource use based on the ERG's clinical advice	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£34,742	£24,630
Exclude unscheduled MRU costs	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£33,569	£23,411

2L: second line, 3L: third line; ADT: androgen deprivation therapy; AE: adverse event; APA: apalutamide; BSC: best supportive care; DOX: docetaxel; ERG: evidence review group; ICER: incremental cost-effectiveness ratio; mHRPC: metastatic hormone relapsed prostate cancer; MRU: medical resource use; PFS2: secondary progression free survival; QALY: quality-adjusted life-years.

6.2 ERG's preferred assumptions

Based on the ERG critique of the company's model discussed in Table 50, we have identified nine key aspects of the company base case with which we disagree. Our preferred model assumptions are the following:

1. **Extrapolation of OS for nmHRPC**: We use the generalised gamma models for OS because they are more consistent with the long-term survival estimates provided by our clinical experts.
2 **Mean health state durations of first, second and third line mHRPC health states**: It is unclear the company's rationale to adjust the health state durations for the proportion of patients not dying in the pre-progression state. Therefore, we assume in our base case to use the unadjusted health state durations (for further discussion, see section 4.2.8.3).
3. **Mean health state duration of third line mHRPC**: We assume that the duration of 3L mHRPC should be based in the time spent in both active treatment and BSC from TA387, i.e. [redacted] for apalutamide plus ADT and [redacted] for ADT alone and docetaxel plus ADT (for further discussion, see section 4.2.8.3).
4. **Health state utilities for second and third line mHRPC health states**: We assume a better approach to not adjust these utilities for the 1L mHRPC utility value, i.e.0.625 for 2L mHRPC and 0.5 for 3L mHRPC (for further discussion, see section 4.2.7.2).
5. **Duration of adverse events' disutilities in the pre-progression health state**: We assume that the disutility from adverse events lasts for two weeks (for further discussion, see section 4.2.7.3).
6. **Duration of adverse events costs for docetaxel**: Docetaxel is given for six cycles and the majority of adverse events occur during this period. Therefore, we assume that applying the costs of docetaxel adverse events for a whole year is not adequate. The ERG applies a duration of six months as our preferred assumption (for further discussion, see section 4.2.8.4).
7. **Neutropenia cost**: We consider the company's input an overestimation and assume that patients experiencing neutropenia would only require an additional outpatient visit and blood test, i.e. £150,16 (for further discussion, see section 4.2.8.4).
8. **Resource use**: To reflect clinical practice, we changed resource use according to the ERG's clinical advice (for further discussion, see section 4.2.8.3 and Appendix 9.6).
9. **Unscheduled MRU costs**: It is unclear the company's rationale to include unscheduled MRU costs since AE disutility costs are already being included. Therefore, we assume to exclude these costs in our base case assumptions (for further discussion, see section 4.2.8.3).

6.2.1 Results from the ERG preferred model assumptions

Table 53 and Table 54 show the cumulative cost-effectiveness results of applying the ERG preferred model assumptions to the corrected company's base case for nmHRPC and mHSPC, respectively. Incorporating the ERG assumptions do not have a significant impact on the overall results for nmHRPC, in which apalutamide plus ADT still dominates ADT alone. For mHSPC, the ICER decreases from £25,002 per QALY to £22,294 per QALY versus ADT alone, but considerably increases from £34,636 per QALY to £49,298 per QALY versus docetaxel plus ADT.

- The change that has the biggest impact on the cost-effectiveness results is the assumption that adverse events costs for docetaxel only lasts 6 months. Using the mean health state duration of third line mHRPC based both on the active treatment and BSC durations from TA387 and using unadjusted health state utilities for second and third line mHRPC also significantly increases the ICER for apalutamide plus ADT versus docetaxel plus ADT.
- Incorporating the remaining ERG assumptions influence the ICER to a lesser extent.

Table 53 Cumulative cost-effectiveness results for ERG's preferred model assumptions for nmHRPC (discounted, PAS price for apalutamide)

Parameter	Treatment	Total costs	Total QALYs	ICER (£/QALY)
Corrected company base case	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ OS extrapolation: jointly fitted generalised gamma	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Unadjusted duration of mHRPC health states	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Mean health state duration for 3L based on the active treatment and BSC durations from TA387	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Unadjusted health state utilities for 2L/3L	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Duration of AE disutilies in the pre progression health state – 2 weeks	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Neutropenia cost – £150.16	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Resource use based on the ERG's clinical advice	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Exclude unscheduled MRU costs	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
ERG preferred model	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates

2L: second line, 3L: third line; ADT: androgen deprivation therapy; AE: adverse event; APA: apalutamide; BSC: best supportive care; ERG: evidence review group; ICER: incremental cost-effectiveness ratio; mHRPC: metastatic hormone relapsed prostate cancer; MRU: medical resource use; OS: overall survival; QALY: quality-adjusted life-years.

Table 54 Cumulative cost-effectiveness results for ERG's preferred model assumptions for mHSPC (discounted, PAS price for apalutamide)

Scenario	Treatment	Total costs	Total QALYs	ICER (£/QALY)	
				APA vs. DOX	APA vs. ADT alone
Corrected company base case	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£34,636	£25,002
+ Unadjusted duration of mHRPC health states	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£34,665	£25,009
+ Mean health state duration for 3L based on the active treatment and BSC durations from TA387	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£38,199	£25,944
+ Unadjusted health state utilities for 2L/3L	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£40,582	£25,096
+ Duration of AE disutilities in the pre progression health state – 2 weeks	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£41,581	£24,267
+ Duration of AE costs for docetaxel – 6 months	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£49,298	£24,267
+ Neutropenia cost – £150.16	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£50,227	£24,086
+ Resource use based on the ERG's clinical advice	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£50,377	£23,763
+ Exclude unscheduled MRU costs	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£49,298	£22,294
ERG preferred model	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£49,298	£22,294

2L: second line, 3L: third line; ADT: androgen deprivation therapy; AE: adverse event; APA: apalutamide; BSC: best supportive care; DOX: docetaxel; ERG: evidence review group; ICER: incremental cost-effectiveness ratio; mHRPC: metastatic hormone relapsed prostate cancer; MRU: medical resource use; QALY: quality-adjusted life-years.

Table 55 and Table 56 show the results from the ERG's preferred base case disaggregated by health state.

Table 55 ERG's preferred base case results disaggregated by health state for nmHRPC (discounted, PAS price for apalutamide)

Outcome	Health state				
	Pre-progression	1L mHRPC	2L mHRPC	3L mHRPC	Newly dead
Apalutamide plus ADT					
Life years	3.19	1.80	0.62	0.65	-
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADT alone					
Life years	1.57	2.04	0.86	1.04	-
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1L: first line; 2L: second line; 3L: third line; ADT: androgen deprivation therapy; ERG: Evidence Review Group; mHRPC: metastatic hormone resistant prostate cancer; nmHRPC: non metastatic hormone resistant prostate cancer; QALYs: quality-adjusted life years.					

Table 56 ERG's preferred base case results disaggregated by health state for mHSPC (discounted, PAS price for apalutamide)

Outcome	Health state				
	Pre-progression	1L mHRPC	2L mHRPC	3L mHRPC	Newly dead
Apalutamide plus ADT					
Life years	3.48	1.04	0.73	0.77	-
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADT alone					
Life years	2.30	1.24	0.47	0.57	-
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel plus ADT					
Life years	2.71	0.96	0.83	1.00	-
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1L: first line; 2L: second line; 3L: third line; ADT: androgen deprivation therapy; ERG: Evidence Review Group; mHSPC: metastatic hormone sensitive prostate cancer; mHRPC: metastatic hormone resistant prostate cancer; QALYs: quality-adjusted life years.					

6.3 Scenario analyses conducted on the ERG's preferred assumptions

We performed a range of scenario analyses with the ERG base case in order to analyse the impact of changing some of the model assumptions in the final cost effectiveness results. Most of the scenarios replicates the company's scenario analysis (as previously described in section 5.2.2). The remaining scenarios were conducted to assess the impact of changing the following model assumptions:

- Use KM data for MFS until week 120 and an extrapolated tail thereafter;
- Use independently fitted curves with log-logistic, log-normal and generalised gamma to extrapolate PFS2 for nmHRPC;
- Use jointly fitted curves with the Gompertz distribution to extrapolate PFS2 for mHSPC;
- Use independently and jointly fitted curves with generalised gamma to extrapolate OS for nmHRPC;
- Using alternative treatment waning start and end points (between 5 and 10 years)
- Using alternative sources to estimate utility values for second and third line mHRPC health states (TA377 and TA580);

- Include age-related disutility for pre-progression health state.

Table 57 presents the results for nmHRPC and Table 58 for mHSPC. The ERG notes:
For nmHRPC

- Apalutamide plus ADT dominates ADT alone in all the scenarios except when the subsequent therapy market shares are based on the SPARTAN trial (ICER increases to £24,176 per QALY) and when using log-logistic and log-normal independently fitted curves to extrapolate MFS (ICER increases to £146 and £203 per QALY, respectively).

For mHSPC

- The ICERs range from £13,732 per QALY (scenario: subsequent therapy market shares from nmHRPC advisory board) to £51,958 per QALY (scenario: subsequent therapy market shares from TITAN trial) for apalutamide plus ADT compared to ADT alone.
- For the comparison against docetaxel plus ADT, the ICERs range from £30,143 per QALY (scenario: mean health state durations for first line mHRPC health state from TA387) to £91,658 (scenario: subsequent therapy market shares from TITAN trial).
- The scenario that lead to a higher increase in the ICER is using the subsequent therapy market shares from the TITAN trial (£51,958 per QALY for apalutamide plus ADT versus ADT alone and £91,658 per QALY versus docetaxel plus ADT).
- Using different survival curves to extrapolate rPFS have also a significant effect on the cost-effectiveness results comparing apalutamide plus ADT versus ADT alone (£34,439 per QALY for exponential, £33,656 per QALY for log-logistic and £35,685 per QALY for log-normal) and apalutamide plus ADT versus docetaxel plus ADT (£79,379 per QALY for exponential, £71,407 per QALY for log-logistic and £78,018 per QALY for log-normal).

Additionally, when comparing apalutamide plus ADT versus ADT alone:

- Using the mean health state durations for first line mHRPC health state from TA387 increases the ICER to £30,217 per QALY.
- The remaining scenarios do not change the ICER more than £5,000 per QALY.

When comparing apalutamide plus ADT versus docetaxel plus ADT:

- Using the unstratified curves as the OS curve fitting approach increases the ICER to £62,174 per QALY.
- Using the log normal survival curve to extrapolate OS decreases the ICER to £36,370 per QALY.

- The remaining scenarios do not change the ICER more than £10,000 per QALY.

Table 57 Scenario analyses using the ERG's preferred model assumptions for nmHRPC (discounted, PAS price for apalutamide)

Scenario	ICER (£/QALY)
ERG preferred model	Dominates
Time horizon: 30 years	Dominates
Time horizon: 20 years	Dominates
Time horizon: 10 years	Dominates
Unadjusted SPARTAN data for one novel therapy rule	Dominates
MFS extrapolation: independently fitted log-logistic	£146
MFS extrapolation: independently fitted log-normal	£203
MFS extrapolation: use KM data and extrapolated tail	Dominates
PFS2 extrapolation: jointly fitted log-logistic	Dominates
PFS2 extrapolation: jointly fitted log-normal	Dominates
PFS2 extrapolation: jointly fitted generalised gamma	Dominates
PFS2 extrapolation: independently fitted log-logistic	Dominates
PFS2 extrapolation: independently fitted log-normal	Dominates
PFS2 extrapolation: independently fitted generalised gamma	Dominates
OS extrapolation: independently fitted generalised gamma	Dominates
OS extrapolation: jointly fitted weibull	Dominates
Mean health state durations from TA387 for 1L mHRPC	Dominates
Treatment waning between 10-15 years	Dominates
Treatment waning between 5-10 years	Dominates
Subsequent therapy market shares: SPARTAN trial	£24,176
Subsequent therapy market shares: nmHRPC advisory board	Dominates
AE disutilities: literature values	Dominates
mHRPC utilities: assumed constant through mHRPC	Dominates
2L/3L mHRPC utility values from TA580	Dominates
2L/3L mHRPC utility values from TA377	Dominates
Include age-related disutility	Dominates
1L: first line; 2L: second line; 3L: third line; ADT: androgen deprivation therapy; AE: adverse event; APA: apalutamide plus ADT; ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; MFS: metastatic-free survival; mHSPC: metastatic hormone sensitive prostate cancer; mHRPC: metastatic hormone resistant prostate cancer; nmHRPC: non metastatic hormone resistant prostate cancer; OS: overall survival; PFS2: secondary progression-free survival; QALYs: quality-adjusted life years.	

Table 58 Scenario analyses using the ERG's preferred model assumptions for mHSPC (discounted, PAS price for apalutamide)

Scenario	ICER (£/QALY) vs. ADT alone	ICER (£/QALY) vs. DOX
ERG preferred model	£22,294	£49,298

Time horizon: 30 years	£22,293	£49,300
Time horizon: 20 years	£22,350	£49,610
Time horizon: 10 years	£24,685	£58,362
rPFS extrapolation: independently fitted exponential	£34,439	£79,379
rPFS extrapolation: independently fitted log-logistic	£33,656	£71,407
rPFS extrapolation: independently fitted log-normal	£35,685	£78,018
PFS2 extrapolation: jointly fitted Gompertz	£24,777	£53,891
OS extrapolation: log-logistic (informed fits)	£22,197	£40,659
OS extrapolation: log-normal (informed fits)	£20,806	£36,370
OS extrapolation: generalised gamma (informed fits)	£21,161	£42,850
OS extrapolation: Gompertz (informed fits)	£25,380	£53,036
OS curve fitting approach: jointly fitted Weibull (unstratified)	£26,224	£62,174
Mean health state durations from TA387 for 1L mHRPC	£30,217	£30,143
Treatment waning between 10-15 years	£22,992	£51,341
Treatment waning between 5-10 years	£25,627	£57,774
Subsequent therapy market shares: TITAN trial	£51,958	£91,658
Subsequent therapy market shares: nmHRPC advisory board	£13,732	£42,504
Utility source: STAMPEDE	£21,969	£49,621
AE disutilities: literature values	£22,319	£48,792
mHRPC utilities: assumed constant throughout mHRPC	£21,378	£55,805
2L/3L mHRPC utility values from TA580	£20,984	£57,096
2L/3L mHRPC utility values from TA377	£22,354	£49,141
Include age-related disutility	£22,984	£51,615
1L: first line; 2L: second line; 3L: third line; ADT: androgen deprivation therapy; AE: adverse event; APA: apalutamide plus ADT; DOX: docetaxel plus ADT; ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; mHSPC: metastatic hormone sensitive prostate cancer; mHRPC: metastatic hormone resistant prostate cancer; nmHRPC: non metastatic hormone resistant prostate cancer; OS: overall survival; QALYs: quality-adjusted life years, rPFS: radiographic progression-free survival.		

6.4 Conclusions on the cost effectiveness evidence

The key issues identified by the ERG in the cost effectiveness evidence are the following:

- Extrapolation of MFS/rPFS survival curves;
- Selection of methods to adjust for treatment switching in the pivotal apalutamide clinical trials;
- Utility values for second and third line mHRPC health states;
- Market share of subsequent therapies for mHRPC;
- Duration of adverse event costs for docetaxel.

As minor issues, the ERG also disagrees with the company about other assumptions (all of them are described in Table 50).

The ERG's preferred model assumptions do not change the dominance of apalutamide plus ADT versus ADT alone for nmHRPC, i.e., apalutamide plus ADT is still cheaper and more effective than ADT alone. However, for mHSPC, our assumptions decrease the ICER for apalutamide plus ADT versus ADT alone to £22,294 per QALY and increases the ICER for apalutamide plus ADT versus docetaxel plus ADT to £49,298 QALY. The overall results are most sensitive to changes in the subsequent therapy market shares, mean health state durations for mHRPC health states and the survival curves to extrapolate PFS and OS.

7 END OF LIFE

The CS does not discuss whether NICE end of life considerations are satisfied. The ERG is of the opinion that apalutamide plus ADT does not meet the first end of life criterion as the life expectancy of patients treated with ADT would normally be greater than 24 months. For nmHRPC, the median OS for patients treated with ADT was 59.89 months in the SPARTAN trial. In the TITAN trial, median OS has not yet been reached. The mean OS for ADT in the company's base case was 4.6 years.

However, there is sufficient evidence to indicate that treatment with apalutamide plus ADT offers an extension of life of more than three months. The median improvement in life expectancy for apalutamide plus ADT for nmHRPC was 14 months. The mean gain in life expectancy for mHSPC was six months for apalutamide plus ADT vs docetaxel plus ADT and 17 months vs ADT alone.

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9 Appendices

9.1 Efficacy outcome definitions in the SPARTAN and TITAN trials

SPARTAN – Efficacy outcome definitions

Endpoints	Outcome definition	Data cut	Used in Economic Model	ERG comments
Primary				
Metastasis-free survival (MFS)	Time from randomisation to the time of the scan that showed first evidence of BICR-confirmed radiographically detectable bone or soft tissue distant metastasis or death due to any cause (whichever occurred earlier)	19th May 2017	Yes	• Appropriate to use an intermediate primary endpoint as prostate cancer has a relatively long disease course. • Case definition is appropriate. BICR used to minimise bias through objective outcome assessment. • Deaths were included as events based on the assumption that they occur at random. This is a reasonable assumption in this setting as deaths prior to metastases are likely to be from unrelated causes.
Secondary				
Overall survival (OS)	Time from randomisation to the date of death due to any cause.	1st Feb 2020	Yes	Appropriate. Considered gold standard. Data are considered mature.
Time to initiation of chemotherapy	Time from randomisation to documentation of a new cytotoxic chemotherapy being administered to the patient (e.g. survival follow-up CRF)	1st Feb 2020	No	• Important clinical outcome from patient perspective as progression to mHRPC and need for chemotherapy may have significant burden on quality of life.. • Measurement based on objective record of drug administration
Time to metastasis (TTM)	Time from randomisation to the time of the scan that showed first evidence of BICR-confirmed radiographically detectable bone or soft tissue distant metastasis (death not included as an event).	19th May 2017	No	This outcome is closely related to MFS but patients who die are censored rather than being included as having events. Censoring at death is likely to be non-informative as deaths prior to

Endpoints	Outcome definition	Data cut	Used in Economic Model	ERG comments
				metastases are likely due to other, unrelated causes.
Progression-free survival	Time from randomisation to first documentation of BICR-confirmed radiographic progressive disease (based on RECIST v1.1) or death due to any cause (whichever occurs first)	19th May 2017	No	• This outcome includes metastases as well as loco-regional progression. • Objective assessment using BICR with standardised criteria (RECIST).
Time to symptomatic progression	Time from randomisation to documentation in the case report form (CRF) of any of the following (whichever occurred earlier): o Development of a skeletal-related event (SRE): pathologic fracture, spinal cord compression, or need for surgical intervention or radiation therapy to the bone o Pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anti-cancer therapy o Development of clinically significant symptoms due to loco-regional tumour progression requiring surgical intervention or radiation therapy	1st Feb 2020	No	• Composite endpoint. ERG notes that these may be relevant as separate outcomes of interest. • These sub-outcomes are largely objectively measured. It is not clear if pain progression alone was considered here or if this also required initiation of a new systemic anti-cancer therapy, or which therapies were considered.
Other				

Endpoints	Outcome definition	Data cut	Used in Economic Model	ERG comments
Second progression-free survival (PFS2)	Time from randomisation to investigator-assessed disease progression (PSA, radiographic, symptomatic, or any combination) during first subsequent anti-cancer therapy or death (any cause) prior to the start of the second subsequent anti-cancer therapy, whichever occurs first	1st Feb 2020	Yes	This is an appropriate endpoint in this setting as it provides further information in the post-progression phase to assess whether earlier survival benefits (i.e. MFS) are sustained following progression and subsequent therapy.
PSA response	Proportion of patients who achieved at least a 50% decline in PSA value from baseline assessed by a central laboratory according to Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria. The PSA response was confirmed by a central laboratory measurement obtained 4 or more weeks later	19th May 2017	No	Centralised measurement to ensure objective assessment using standardised criteria.
Time to PSA progression	Assessed at the time of the primary analysis of MFS according to the PCWG2 criteria	19th May 2017	No	Centralised measurement to ensure objective assessment.

BICR: blinded independent central review; CRF: case report form; mHRPC metastatic hormone-relapsed prostate cancer; PCWG2: Prostate Cancer Working Group 2; PSA: prostate-specific antigen; SRE skeletal-related event
RECIST: Response Evaluation Criteria in Solid Tumors
Source: CS Table 5 and 6, section 2.7.1-2.7.3

TITAN – Efficacy outcome definitions

Endpoints	Outcome definition	Data cut	Used in Economic Model	ERG comments
Primary				
Radiographic progression - free survival (rPFS)	Time from randomisation to the time of first evidence of radiographic progression identified by bone scan, or for soft tissue lesions by CT or MRI, as defined by modified RESIST 1.1 criteria and assessed by the investigator. A more precise definition is detailed in CS Table 6.	23rd Nov 2018	Yes	Standardised criteria (RECIST) have been used to determine progression and a BICR audit based on 60% of patients selected at random had 85% concordance rate with investigator assessment.
Overall survival (OS)	Time from randomisation to the date of death due to any cause.	23rd Nov 2018	Yes	Appropriate; gold standard. Data immature in current submission.
Secondary				
Time to pain progression	Time from randomisation to an increase by 2 points from baseline in the BPI-SF worst pain intensity (item 3) observed at two consecutive evaluations ≥3 weeks apart; with an average worst pain score of >4 in patients who had no decrease in opioids or initiation of chronic opioids, whichever occurs first	23rd Nov 2018	No	Appropriate choice of outcome. Potential for measurement error due to subjective nature of measuring pain but not anticipated to be differential between treatment arms.
Time to initiation of chemotherapy	Time from randomisation to date of initiation of cytotoxic chemotherapy	23rd Nov 2018	No	Important clinical outcome from patient perspective as progression to mHRPC and need for chemotherapy may have greater impact on quality of life. Objective measurement.

Endpoints	Outcome definition	Data cut	Used in Economic Model	ERG comments
Time to skeletal-related event	Time from randomisation to occurrence of symptomatic pathological fracture, spinal cord compression, radiation to bone, or surgery to bone.	23rd Nov 2018	No	Objective measurement.
Time to chronic opioid use	Time from randomisation to first date of confirmed chronic opioid use.	23rd Nov 2018	No	Based on objective record of prescription.
Other				
Second progression-free survival (PFS2)	Time from randomisation to date of first occurrence of disease progression on first subsequent prostate cancer therapy or death (any cause), whichever occurs first	23rd Nov 2018	Yes	This is an appropriate endpoint in this setting as it provides further information in the post-progression phase to assess whether earlier survival benefits (i.e. rPFS) are sustained following progression and subsequent therapy. Data immature in current submission.
Overall response	Defined by RECIST 1.1	23rd Nov 2018	No	Based on complete response according to standardised criteria.
Time to PSA progression	Time from randomisation to to PSA progression was based on PCWG2 criteria	23rd Nov 2018	No	Centralised measurement to ensure objective assessment.
Prostate cancer specific survival	Time from randomisation to prostate cancer related death	23rd Nov 2018	No	Data are immature.

BICR: blinded independent central review; CRF: case report form; CT computerised topography; mHRPC metastatic hormone-relapsed prostate cancer; MRI magnetic resonance imaging; PCWG2: Prostate Cancer Working Group 2; PSA: prostate-specific antigen; RECIST: Response Evaluation Criteria in Solid Tumors
Source: CS Table 5 and 6

9.2 Comparative analysis of patient populations in COU-AA-302 and COU-AA-301 versus the SPARTAN population

The characteristics of patients from the COU-AA-302 and COU-AA-301 trials were compared with the characteristics reported for the SPARTAN trial. As shown in **Error! Reference source not found.** patients from the COU-AA-302 trial[62] had mHRPC and had not received prior chemotherapy. Patients in the COU-AA-302 trial therefore appear to be a better match to SPARTAN trial participants than those from the COU-AA-301 trial[63] where all patients had received prior docetaxel.

Table A Comparison of SPARTAN, COU-AA-302 and COU-AA-301 trials patient characteristics

	SPARTAN				**COU-AA-302**				**COU-AA-301**			
Patient population at study entry	High-risk nmHRPC, no prior chemotherapy[a]				mHRPC, no prior chemotherapy				mHRPC progressing after docetaxel			
	Apalutamide plus ADT		Placebo plus ADT		Abiraterone plus prednisone		Prednisone		Abiraterone plus prednisone		Prednisone	
Age, median years (range)	74.0 (48-94)		74.0 (52-97)		71 (65-77)		70 (63-76)		69 (42-95)		69 (39-90)	
Age categorization												
≥ 75 and < 79	23.0%		20.0%		34%		30%		28%		28%	
≥ 80 and < 84	17.9%		17.7%									
> 85	7.9%		9.5%									
Gleason score at initial diagnosis	< 7	19.4%	< 7	18.6%	≤7	46%	≤7	50%				
	=7	37.1%	=7	37.7%					≤8	49%	≤8	46%
	> 7	43.5%	> 7	43.7%	≥8	54%	≥8	50%	≥8	51%	≥8	54%
ECOG performance status score	0	77.3%	0	77.8%					0 or 1	90%	0 or 1	89%
	1	22.7%	1	22.3%								

[a] except in adjuvant/neoadjuvant setting

9.3 Estimation of counterfactual survival time

Table B Estimation of counterfactual survival time for the comparison of apalutamide versus placebo

Patient sub-population	Estimation of the counterfactual survival time, CF_{UK}	Survival estimates adjusted	Trials	Arm(s)
Patients who switched to second novel treatment	CF_{UK}=time to switch + time after switch * exp(ψ^{ST})[a]	OS, PFS2	SPARTAN	APA+ADT placebo+ADT
Patients who switched (crossed over) from placebo to apalutamide	CF_{UK}=time to crossover + time after crossover * exp(ψ^{a})[b]	OS, PFS2	SPARTAN	placebo+ADT
	CF_{UK}^{RC}=minimum (CF_{UK}, exp(ψ^{ST})*C)[c]	OS, PFS2	SPARTAN	APA+ADT placebo+ADT
Non-switcher patients	CF_{UK}=observed time to event data	OS, PFS2	SPARTAN, TITAN	APA+ADT placebo+ADT

Source: CS Appendix R.1 page 854

APA apalutamide

a exp(ψ^{ST}) is the shrinkage factor associated with subsequent enzalutamide/abiraterone use estimated following Diels et al.[29]

b exp(ψ^{a}) is the shrinkage factor attributed to apalutamide, estimated using RPSFTM.

c CF_{UK}^{RC} is counterfactual re-censored survival time, where C denotes the time between randomization to analysis cut-off date/censor date (CS Appendix R.1 page 856).

9.4 ERG review of the searches conducted by the company for the informed fits analyses

The SLR to identify appropriate studies for the company's informed fits analysis is briefly reported in CS Appendix S. For both prostate cancer indications, the CS states they are looking for historical data from ADT arms of other clinical trials (CS Appendix S). It does not define historical data, and we assume that this means studies which have completed and published results, rather than studies in progress. We also assume that they are looking for comparative studies (i.e. not single-arm or cohort studies) but we do not know if they did not include single-arm studies. ERG comments on the SLR specific to each indication are below.

nmHRPC

- The company use a recent (2018 accepted, 2019 fully published) systematic review on time to event outcomes in nmCRPC.[43]The ERG believes the population and outcomes are relevant to the informed fits analysis and that using a recent systematic review to identify relevant studies is appropriate.
- As for the mHSPC SLR above, there is limited documentation reported in the CS: there is no PICO, no inclusion or exclusion criteria, no record of which databases or registries were searched, no search strings, no PRISMA flow diagram, no excluded studies listed, and no reviewer methods described. We do not know how the Aly 2018 systematic review was identified, and, as above for the mHSPC search, without this documentation we cannot verify, assess or replicate the search, nor screen results for any search we might perform ourselves.
- Three clinical trials with a similar patient population to SPARTAN were identified from Aly et al.[43](CS Table S.2). The ERG assumes that *high-risk* nmHRPC might be one of the inclusion criteria because the reason for not searching patient registries and real-world data was because the company believe it would not be possible to separate high-risk from low-risk patients in those types of study.

Table S.3. shows the baseline characteristics alongside those of the three historical trials identified from Aly et al. Baseline characteristics were not reported for the three historical trials for many of the reported SPARTAN trial population characteristics, this makes comparison difficult. However, from CS Table S.3 we can see that:

- The three historical trials had a higher proportion of white participants than the SPARTAN trial (over 80% vs 66%).

- ECOG performance status at baseline was similar in the SPARTAN trial and the single historical trial (Smith 2012) that reported this characteristic.
- Gleason score at initial diagnosis appears similar between the SPARTAN trial and the Nelson 2008 trial but the other two historical trials (Smith 2005 and Smith 2012) appear to have a lower proportion of participants with a Gleason score >7 (approximately 30% compared with 43% in SPARTAN).

The ERG carried out a citation search on the company identified systematic review, Aly 2018, and found three citations. Two are on alkaline phosphatase values and on radiotherapy, however, one is a systematic review and meta-analysis of systemic management for nmCRPC. It is published too recently to have been included in the company's search.

mHSPC

- We know that 19 studies were identified, of which seven were included. All 19 studies, and reasons for exclusion, are reported in CS Table S.1.
- The search is inadequately documented: there is no PICO template, no inclusion and exclusion criteria, no record of which databases or registries were searched, no search strings, no PRISMA flow diagram, and no reviewer methods described. Without these we cannot verify, assess or replicate the search, nor screen results for any search we might perform ourselves.
- The CS describes the population as patients with "mHSPC-like" diseases. This is unclear, the ERG does not know if that means any prostate cancer, any metastatic prostate cancer, or includes any other disease.
- The CS describes pooling IPD from the seven included studies, therefore the ERG could assume that reporting Kaplan-Meier survival estimates is one of the inclusion criteria. The reasons for exclusion in Table S.1 could inform ERG of some exclusion criteria, but not enough to assess or replicate the searches or screening.
- Several studies were excluded because they were an "older study" (range 1986-2009), from which we could assume a date limit within the inclusion criteria but not the searches.

The ERG carried out a brief targeted search of the Scopus database (because it includes records from both Medline and Embase) only for an mHSPC population (not “mHSPC-like”), a few relevant outcomes and ADT, as described in the search string below.

- Scopus search string: TITLE-ABS-KEY (hspc OR "metastatic hormone-sensitive prostate cancer" OR "metastatic hormone-naive prostate cancer" OR "metastatic castrate-sensitive prostate cancer" OR "metastatic castration-sensitive prostate cancer") AND TITLE-ABS-KEY (("time" PRE/1 (event OR "bone metastasis" OR metastasis OR progression)) OR "clinical outcome" OR "survival time" OR "overall survival") AND TITLE-ABS-KEY (adt PRE/0 (arm OR only OR alone))

This search identified 34 publications, one of which is a systematic review of combination therapies compared to ADT alone. This systematic review is published too recently for the company to have missed it in their search, but it is potentially useful to the ERG in identifying relevant studies.

ERG conclusion

Lack of documentation of these SLRs forces the ERG to make assumptions about, for example, the population and the inclusion/exclusion criteria; and there remain things, such as which sources were searched, that is unclear. Therefore, we are unable to assess whether any relevant studies might have been missed. Some brief targeted searching by the ERG identified two systematic reviews that could be a potential source of relevant evidence.

9.5 Model functionality issues

Table A Model functionality issues (amended by the ERG)

Issue	Cell formula	Original formula [a]	Corrected formula [a]	ERG comments
1	Subs therapy costs!O138: Q140	=$E129*O88***Parameters!S327:** $E131*Q90***Parameters!Y335**	=$E129*O88***Parameters!S336:** $E131*Q90***Parameters!S344**	These corrections have a minor impact on the final results.
2	PF_DOX!AJ9:AM9	=AJ8*((**$AE$9**/(1-p_con_preprog_events_DOX))/$AN$8): AM8*((**$AE$9**/(1-p_con_preprog_events_DOX))/$AN$8)	=AJ8*((**SUM($AE$9:$AF$9)**/(1-p_con_preprog_events_DOX))/$AN$8): AM8*((**SUM($AE$9:$AF$9)**/(1-p_con_preprog_events_DOX))/$AN$8)	The formulas used for docetaxel are different from the formulas used for apalutamide and ADT. These corrections have some impact on the final results.
3	PF_APA!AS14: AS1662	=**AL13*($AL$10-Y14):AL1661*($AL$10-Y1662)**	=**MAX(AM14-AM13,0): MAX(AM1662-AM1661,0)**	Incident patients on third line mHRPC are greater than incident patients on second line, which is implausible (see section 4.2.6.1). Therefore, the ERG suggests the use of a new formula. These corrections have some impact on the final results.
4	PF_ADT!AS14: AS1662	=**AL13*($AL$10-Y14):AL1661*($AL$10-Y1662)**		
5	PF_DOX!AS14: AS16	**=0**		
6	PF_DOX!AS17: AS1662	=**AL16*$AL$10:AL1661*$AL$10**		
7	PF_APA!AW14: AW1662,	=1/((1+**con_DR_LYs**)^$N14): 1/((1+**con_DR_LYs**)^$N1662)	=1/((1+**p_con_DR_LYs**)^$N14): 1/((1+**p_con_DR_LYs**)^$N1662)	These corrections impact the deterministic sensitivity analysis results only.
8	PF_APA!AX14: AX1662,	=1/((1+**con_DR_QALYs**)^$N14): 1/((1+**con_DR_QALYs**)^$N1662)	=1/((1+**p_con_DR_QALYs**)^$N14): 1/((1+**p_con_DR_QALYs**)^$N1662)	
9	PF_APA!AY14: AY1662,	=1/((1+**con_DR_costs**)^$N14): 1/((1+**con_DR_costs**)^$N1662)	=1/((1+**p_con_DR_costs**)^$N14): 1/((1+**p_con_DR_costs**)^$N1662)	

Issue	Cell formula	Original formula [a]	Corrected formula [a]	ERG comments
10	PF_DOX!BG14: BG1662	=BA14*(final.util_preprog+(IF(con_AE_disutils_source="Utility regression parameters",final.util_AE_dox***AU16**,final.util_AE_dox))+(IF(N14>1,0,p_util_TTO_dox_dec))): BA1662*(final.util_preprog+(IF(con_AE_disutils_source="Utility regression parameters",final.util_AE_dox***AU1664**,final.util_AE_dox))+(IF(N1662>1,0,p_util_TTO_dox_dec)))	=BA14*(final.util_preprog+(IF(con_AE_disutils_source="Utility regression parameters",final.util_AE_dox***AU14**,final.util_AE_dox))+(IF(N14>1,0,p_util_TTO_dox_dec))): BA1662*(final.util_preprog+(IF(con_AE_disutils_source="Utility regression parameters",final.util_AE_dox***AU1662**,final.util_AE_dox))+(IF(N1662>1,0,p_util_TTO_dox_dec)))	These corrections have a minor impact on the final results.
ADT: androgen deprivation therapy, APA: apalutamide plus ADT, DOX: docetaxel plus ADT, ERG: evidence review group, ICER: incremental cost-effectiveness ratio, mHRPC: metastatic hormone refractory prostate cancer. [a] The differences between the original formula and the corrected one are presented in bold.				

Table B Model functionality issues (not amended by the ERG)

Issue	Cell formula	Original formula	Corrected formula	ERG comments
1	Drug costs!H22	=**p_dc_pack_aap_1L***(1-con_PAS_aap_2L)	=**p_dc_pack_aap_2L***(1-con_PAS_aap_2L)	This correction could have an impact on the final results if the price of first line abiraterone is different from the price of second-line abiraterone.
2	Subs therapy costs!C121	=$E103***C88**	=$E103***C91**	These cells don't seem to be used in the model – These corrections have no impact on the final results.
3	Subs therapy costs!D121	=$E103***D88**	=$E103***D91**	

Issue	Cell formula	Original formula	Corrected formula	ERG comments
4	Subs therapy costs!E121	=$E103***E88**	=$E103***E91**	
5	Subs therapy costs!I120	=**$E105***I87	=**$E102***I87	
6	Subs therapy costs!I121	=**$E106*I88**	=**$E103*I91**	
7	Subs therapy costs!J120	=**$E105***J87	=**$E102***J87	
8	Subs therapy costs!J121	=**$E106*J88**	=**$E103*J91**	
9	Subs therapy costs!K120	=**$E105***K87	=**$E102***K87	
10	Subs therapy costs!K121	=**$E106*K88**	=**$E103*K91**	
11	Subs therapy costs!O121	=**$E103*O88**	=**$E106*O91**	
12	Subs therapy costs!P121	=**$E103*P88**	=**$E106*P91**	
13	Subs therapy costs!Q121	=**$E103*Q88**	=**$E106*Q91**	
14	Subs therapy costs!O146	=$C129*O88***Parameters!S327**	=$C129*O88***Parameters!S336**	These cells don't seem to be used in the model – These corrections have no impact on the final results.
15	Subs therapy costs!O147	=$C130*O89***Parameters!S328**	=$C130*O89***Parameters!S337**	

Issue	Cell formula	Original formula	Corrected formula	ERG comments
16	Subs therapy costs!O148	=$C131*O90***Parameters!S329**	=$C131*O90***Parameters!S338**	
17	Subs therapy costs!P146	=$C129*P88***Parameters!S330**	=$C129*P88***Parameters!S339**	
18	Subs therapy costs!P147	=$C130*P89***Parameters!S331**	=$C130*P89***Parameters!S340**	
19	Subs therapy costs!P148	=$C131*P90***Parameters!S332**	=$C131*P90***Parameters!S341**	
20	Subs therapy costs!Q146	=$C129*Q88***Parameters!S333**	=$C129*Q88***Parameters!S342**	
21	Subs therapy costs!Q147	=$C130*Q89***Parameters!S334**	=$C130*Q89***Parameters!S343**	
22	Subs therapy costs!Q148	=$C131*Q90***Parameters!S335**	=$C131*Q90***Parameters!S344**	
23	Results!K13	=IF(J13="Dominated","Strictly Dominated",IF(J13>J14,"**Extendedly dominated**",""))	=IF(J13="Dominated","Strictly Dominated",IF(J13>J14,"**Extendedly dominates**",""))	The ERG notes that docetaxel should not be considered extendedly dominated as ICER DOX vs. ADT < ICER APA vs. ADT. The ERG notes that this incorrection does not exist in the CS.
24	Results!L13	=IF(OR(K13="**Extendedly dominated**",K13="Strictly dominated"),K13,(C13-C12)/(E13-E12))	=IF(OR(K13="**Extendedly dominates**",K13="Strictly dominated"),K13,(C13-C12)/(E13-E12))	
25	Results!L14	=IF(OR(K14="**Extendedly dominated**",K14="Strictly dominated"),K14,IF(OR(K13="**Extendedly**	=IF(OR(K14="**Extendedly dominates**",K14="Strictly dominated"),K14,IF(OR(K13="**Extendedly**	

Issue	Cell formula	Original formula	Corrected formula	ERG comments
		dominated",K13="Strictly dominated"),(C14-C12)/(E14-E12),(C14-C13)/(E14-E13)))	**dominates**",K13="Strictly dominated"),(C14-C12)/(E14-E12),(C14-C13)/(E14-E13)))	
26	Results!C90	=TRANSPOSE(**E64:E66**)	=TRANSPOSE(**E58:E60**)	These corrections have no impact on the final results but could lead to misinterpretations.
27	Results!D90	=TRANSPOSE(**E64:E66**)	=TRANSPOSE(**E58:E60**)	
28	Results!E90	=TRANSPOSE(**E64:E66**)	=TRANSPOSE(**E58:E60**)	
29	OWSA!P84	=IF(B84="","",((**J84-L84**)*con_WTP)-(**I84-K84**))	=IF(B84="","",((**D84-F84**)*con_WTP)-(**C84-E84**))	These cells don't seem to be used in the model – These corrections have no impact on the final results.
30	OWSA!T84	=IF(B84="","",**L84***con_WTP-**K84**)	=IF(B84="","",((**J84-L84**)*con_WTP)-(**I84-K84**))	
31	OWSA!V84	=IF(B84="","",**N84***con_WTP-**M84**)	=IF(B84="","",((**J84-N84**)*con_WTP)-(I**84-M84**))	
ADT: androgen deprivation therapy, APA: apalutamide plus ADT, DOX: docetaxel plus ADT, ERG: evidence review group, ICER: incremental cost-effectiveness ratio.				

9.6 ERG alternative medical resource use estimates

Table A nmHRPC: medical resource use suggested by the clinical experts advising the ERG [a]

Resource use	Apalutamide plus ADT			ADT alone		
	% use	Frequency (first 3 months)	Frequency per cycle (after 3 months)	% use	Frequency (first 1 year)	Frequency per cycle (after 1 year)
CT scan	**10%**	1 every 52 weeks	1 every 52 weeks	**10%**	**1 every 26 weeks**	**1 every 26 weeks**
Bone scan	**10%**	1 every 52 weeks	1 every 52 weeks	**10%**	**1 every 26 weeks**	**1 every 26 weeks**
PSA test	100%	1 every 4 weeks	1 every 12 weeks	100%	1 every 12 weeks	1 every 9 weeks
Testosterone	100%	1 every 52 weeks	1 every 52 weeks	100%	1 every 52 weeks	1 every 52 weeks
Liver function test	33%	1 every 4 weeks	1 every 12 weeks	33%	1 every 12 weeks	1 every 9 weeks
Kidney function test	33%	1 every 4 weeks	1 every 12 weeks	33%	1 every 12 weeks	1 every 9 weeks
FBC	33%	1 every 4 weeks	1 every 12 weeks	33%	1 every 12 weeks	1 every 9 weeks
Oncologist OP visit	100%	1 every 12 weeks	1 every 12 weeks	100%	1 every 12 weeks	1 every 12 weeks
MRI	5%	**1 every 26 weeks**	**1 every 26 weeks**	5%	1 every 12 weeks	1 every 12 weeks
GP visit	100%	1 every 12 weeks	1 every 12 weeks	100%	1 every 12 weeks	1 every 12 weeks
CNS	33%	1 every 26 weeks	1 every 26 weeks	33%	1 every 26 weeks	1 every 26 weeks
PSMA-PET	**50%**	1 every 52 weeks	1 every 52 weeks	**50%**	1 every 52 weeks	1 every 52 weeks
Urologist/ Oncologist	**0%**	1 every 4 weeks	1 every 4 weeks	**0%**	1 every 12 weeks	1 every 12 weeks
Nurse OP visit	**100%**	**1 every 12 weeks**	**1 every 12 weeks**	**100%**	**1 every 12 weeks**	**1 every 12 weeks**

[a] The changes between this table and CS Table 78 are underlined and in bold.
ADT: androgen deprivation therapy; CNS: central nervous system; CT: computed tomography; ERG: Evidence Review Group; FBC: full blood count; GP: general practitioner; MRI: magnetic resonance imaging; nmHRPC: nonmetastatic hormone resistant prostate cancer; OP: outpatient; PSA: prostate-specific antigen; PSMA-PET: prostate-specific membrane antigen positron emission tomography.

Table B mHSPC: medical resource use suggested by the clinical experts advising the ERG [a]

Resource use	Apalutamide plus ADT			ADT alone			Docetaxel plus ADT	
	% use	Frequency (first 3 months)	Frequency per cycle (after 3 months)	% use	Frequency (first 1 year)	Frequency per cycle (after 1 year)	% use	Frequency
CT scan	100 %	1 every 52 weeks	1 every 52 weeks	100 %	1 every 52 weeks	1 every 52 weeks	100 %	1 every 18 weeks
Bone scan	100 %	1 every 52 weeks	1 every 52 weeks	100 %	1 every 52 weeks	1 every 52 weeks	100 %	1 every 52 weeks
PSA test	100 %	**1 every 4 weeks**	1 every 12 weeks	100 %	1 every 12 weeks	1 every 12 weeks	100 %	1 every 3 weeks
Testosterone	**0%**	1 every 12 weeks	1 every 12 weeks	**0%**	1 every 12 weeks	1 every 12 weeks	**0%**	1 every 3 weeks
Liver function test	100 %	**1 every 26 weeks**	**1 every 26 weeks**	100 %	**1 every 26 weeks**	**1 every 26 weeks**	100 %	1 every 3 weeks
Kidney function test	100 %	**1 every 4 weeks**	1 every 12 weeks	100 %	1 every 12 weeks	1 every 12 weeks	100 %	1 every 3 weeks
FBC	100 %	**1 every 4 weeks**	1 every 12 weeks	100 %	1 every 12 weeks	1 every 12 weeks	100 %	1 every 3 weeks
Oncologist visit	100 %	**1 every 26 weeks**	**1 every 26 weeks**	100 %	**1 every 26 weeks**	**1 every 26 weeks**	100 %	**1 every 6 weeks**
GP visit	**100 %**	**1 every 26 weeks**	**1 every 26 weeks**	**100 %**	**1 every 26 weeks**	**1 every 26 weeks**	**100 %**	**1 every 6 weeks**

[a] The changes between this table and CS Table 77 are underlined and in bold.
ADT: androgen deprivation therapy; CT: computed tomography; ERG: Evidence Review Group; FBC: full blood count; GP: general practitioner; mHSPC: metastatic hormone sensitive prostate cancer; PSA: prostate-specific antigen.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG Responses to the Company's Factual Error Check Pro-forma

Apalutamide for treating prostate cancer [ID1534]

Issue 1 Selection of methods to adjust for treatment switching in the pivotal apalutamide clinical trials (nmHRPC and mHSPC)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 17 of the ERG report it states: "*A range of adjustment methods for treatment switching are available, however the company did not regard them appropriate for their data."*	The proposed amendment is to change the wording to: *"A range of adjustment methods for treatment switching are available. The company considered RPSFTM to be suitable for SPARTAN and naïve censoring, RPSFTM and IPCW to be suitable for TITAN."*	This statement is factually inaccurate as the IPCW and naïve censoring were presented as additional approaches for TITAN in Appendix R.3.2 and include both naïve censoring, IPCW and RPSFTM.	We have removed that sentence and replaced with this: "A range of available adjustment methods for treatment switching were considered for their appropriateness to the available trial data and a justification given for the inclusion/exclusion of each".

Issue 2 Selection of methods to adjust for treatment switching in the pivotal apalutamide clinical trials (nmHRPC and mHSPC)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 17 of the ERG report it states: *"Selection of a single adjustment method without presenting results based on alternative methods prohibits a fully informed committee consideration of the available evidence."*	Please remove this statement.	This statement is factually inaccurate as IPCW was presented for mHSPC in Appendix R.3.2. IPCW was also considered for nmHRPC but its exclusion was clearly justified in Appendix R.1.	Our point was that there is no presentation of cost effectiveness results based on all the alternative methods, (notwithstanding the justifications given for exclusion). We have edited the text in Issue 1 and it now says "Treatment effect estimates can vary widely according to the adjustment methods chosen (and the assumptions therein). Cost effectiveness scenario analyses based on the alternative adjustment methods would indicate whether the ICERs are sensitive to different assumptions about treatment switching and allow a fully-informed committee consideration of the available evidence"

Issue 3 Selection of methods to adjust for treatment switching in the pivotal apalutamide clinical trials (nmHRPC and mHSPC)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 17 of the ERG report it states: *"Scenario analyses based on the alternative adjustment methods would indicate whether the ICERs are sensitive to different assumptions about treatment switching. Also, an additional modified RPSFTM analysis with re-censoring is recommended, based on the methodological literature."*	Please remove this statement	This statement is factually inaccurate as results using RPSFTM with re-censoring are presented in Appendices R.2 for SPARTAN and R.3 for TITAN. The impact on cost-effectiveness of using RPSFTM is minimal given the hazard ratios generated using the two approaches are virtually identical as shown in the following tables in the Appendix R. SPARTAN OS, Table R.7 SPARTAN PFS2, Table R.9 TITAN OS, Table R.14 TITAN PFS2, Table R.15	We have now removed the statement about recensoring. See our response to Issue 2 regarding the statement on scenario analyses.

Issue 4 Treatment pathway for mHSPC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 33 of the ERG report it states: *"The CS states that ADT is not a life-prolonging treatment for patients with mHSPC, however*	The proposed amendment is to change the wording to: *"The CS states that ADT is not a life-prolonging treatment for patients with mHSPC. This is explicitly supported by the reference cited in*	The statement is factually inaccurate as it is misinterpreting absolute values of median overall survival as evidence of overall survival benefit for ADT. This is not the case. Indeed, another reference	After rereading the cited references the ERG is still of the opinion that there is more uncertainty about any effect of ADT on survival in patients with mHSPC than the wording in the

the ERG does not believe that this is supported by the references the company cites. Indeed, one of these references, Aly 2015 et al.[1] states that "median overall survival attributed to ADT in metastatic prostate cancer is heterogeneous and ranges from 23 to 37 months from diagnosis to death".	*CS, Sharifi et.al. 2005 which states that: "ADT has clear quality-of-life benefits but has not been shown to have survival benefits".*	cited in the CS, Sharifi et.al. 2005 states that: *"ADT has clear quality-of-life benefits but has not been shown to have survival benefits."*	CS implies. Whilst Sharifi et al. 2005 do state *"ADT has clear quality-of-life benefits but has not been shown to have survival benefits"* they also state *"However, it is not clear whether there is an improvement in long-term survival".* The ERG has amended the text to indicate that we believe it is more appropriate to state that it is not clear whether ADT improves survival in patients with mHSPC.

Issue 5 Definition of the decision problem

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 35 of the ERG report it states: *"However, clinical effectiveness data are not presented separately for these subgroups and it is not explicitly stated that the trial results are applicable to docetaxel ineligible patients."*	The proposed amendment is to change the wording to: *"However, clinical effectiveness data are not presented separately for these subgroups."*	This statement is factually inaccurate as the applicability of the trial results to this subgroup is addressed in Section B.2.6 of the CS which states: "*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*	Our point is that it is not explicitly stated upfront in the company submission (Document B) that the results of TITAN are intended to represent docetaxel ineligible patients. This only becomes apparent to the reader further into the submission (e.g. B.2.6). Until that point it is not obvious that TITAN represents both docetaxel eligible and ineligible patients. We have made a minor change

		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 (See Section B.2.13).* 3. *Clinicians have stated that they are comfortable prescribe apalutamide to these patients, whose only treatment option is ADT alone."*	to our text to make our point clearer. "However, clinical effectiveness data are not presented separately for these subgroups and it is not explicitly stated in the decision problem or the formative sub-sections of the clinical effectiveness section (B.2) that the TITAN trial results are intended to be applicable to docetaxel ineligible patients".

Issue 6 Summary of trial characteristics

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 45 of the ERG report it states: *"Number not reported in CS"*	The proposed amendment is to change the wording to: *"Number not reported in CS as data was not available at the time of the first interim analysis."*	This statement is misleading. This information was not reported in the CS as crossover was only recommended at trial unblinding following analysis of the first interim analysis data. As such data on cross-over will only be available at final analysis.	We have amended the statement as requested.

Issue 7 Clinical heterogeneity in the docetaxel trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 88 of the ERG report it	Please remove this statement.	This statement is factually inaccurate as the potential impact of	The statement has been

states: *"Beyond this the CS does not comment on the likelihood of clinical heterogeneity amongst the docetaxel trials or between the docetaxel trials and the apalutamide trial (TITAN)."*		heterogeneity in the docetaxel trials was presented in Table 44 of the CS.	removed.

Issue 8 Adjusting survival estimates for STAMPEDE

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 90 of the ERG report it states: *"The company would not be able to adjust the survival estimates in the economic model unless they had access to IPD (which they did for the STAMPEDE trial)."*	Please remove the part of the statement that reads: *"(which they did for the STAMPEDE trial)."*	This statement is factually inaccurate as it suggests that Janssen can perform any analyses they wish on the STAMPEDE data. Contrary to this view, the contract between Janssen and the STAMPEDE group does not allow Janssen to conduct adjustments on survival estimates on these data.	We have amended the statement as requested.

Issue 9 Source of utility values for the second and third line mHRPC health states

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 21 of the ERG report it states: *"Clarification is needed from the company as to why utility values from NICE TA387 are more appropriate for patients with*	The proposed amendment is to change the wording to: *"The company used utility values from TA387, noting that this approach was consistent with the Committee's preferred analysis in the submission for abiraterone for treating newly*	The ERG's statement doesn't acknowledge the fact that rationale was provided during the submission process. The ERG also recommends testing scenario analyses using data from TA377[2]	We have reworded the text to make our point clearer: "We consider it is unlikely that there will be much, if any, additional published utility values for mHRPC not already

mHRPC than those from NICE TA580 and NICE TA377." This statement does not acknowledge the rationale provided in the company submission and the answer provided in response to the ERG's question at the clarification questions stage.	*diagnosed high-risk mHSPC (ID945). Further clarification for the use of values from TA387 was provided by the company at the clarification questions stage. It was noted that these values were also selected as they reported a complete set of utility values for the 1L, 2L and 3L mHRPC health states in a similar patient population and the values were also similar to those reported in TA377."*	and TA580.[3] However, the values from TA377 are almost identical to those reported in TA387[4], and some of the values from TA580 were redacted in the NICE submission documentation and were therefore not available to the company.	used in previous NICE prostate cancer appraisals. Exploration of existing evidence (e.g. NICE TA580 and NICE TA377) could be informative"

Issue 10 Mean health state durations

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 23 of the ERG report it states: *"The company's rationale to adjust the health state durations for the proportion of patients not dying in the pre-progression state is unclear. Therefore, we use the unadjusted health state durations."* However, clear rationale for this adjustment was provided in the company submission: *"Given that TA387 investigated*	The proposed amendment is to change the wording to: *"The company adjusted the health state durations for the proportion of patients not dying in the pre-progression state. This was because TA387 investigated patients from the point at which they were diagnosed with mHRPC, the mean post-progression survival from the model was estimated by taking the predicted mean life years from the mHRPC health states and dividing this value by the proportion of patients who were assumed to experience disease*	Clear justification for this adjustment was provided in Section B.3.3.7.2 of the company submission. The mean health state durations from TA387[4] capture the mean time from 1L mHRPC, whereas the post-progression survival times in the model capture the average time spent in post-progression survival from the mHSPC or nmHRPC health states. Therefore, these values are not using the same baseline timepoint and are therefore not comparable. Therefore, an adjustment is made to capture the average post-progression survival time	The text has been changed as follows: The ERG is unclear on the need to adjust the health state durations for the proportion of patients not dying in the pre-progression state, as assumed by the company. Therefore, we use the unadjusted health state durations.

patients from the point at which they were diagnosed with mHRPC, the mean post-progression survival from the model was estimated by taking the predicted mean life years from the mHRPC health states and dividing this value by the proportion of patients who were assumed to experience disease progression prior to death. These proportions were estimated for SPARTAN and TITAN, and were estimated by dividing the reported number of MFS/rPFS events that were deaths rather than progressions, by the total number of deaths in the studies."	*progression prior to death."*	of patients who did not die prior to disease progression. This ensures that the values from TA387 and the cost-effectiveness model are comparable.	

Issue 11 mHSPC patient population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 34 of the ERG report it states: *"For the mHSPC population a distinction can be made between newly diagnosed and primary progressed patients (and, as already described, the mHSPC patient group is a heterogenous population in other respects too). It is known that newly diagnosed patients have a poorer prognosis than patients with primary progressive mHSPC. Therefore, whilst there is justification for a subgroup analysis of newly diagnosed mHSPC patients the company haven't commented on the feasibility of*	The proposed amendment is to change the wording to: "*For the mHSPC population a distinction can be made between newly diagnosed and primary progressed patients (and, as already described, the mHSPC patient group is a heterogenous population in other respects too). It is known that newly diagnosed patients have a poorer prognosis than patients with primary progressive mHSPC. However, feedback from*	The ERGs statement that there is justification for a sub-group analysis appears to contradict clinical feedback which notes that the patient population in the TITAN trial is reflective of patients in UK practice.	Not a factual error, no change made.

this." However, the company did not comment on the feasibility of this sub-group analysis as feedback from UK clinical experts stated that the characteristics of patients in TITAN were broadly reflective of patients in UK clinical practice, and therefore no sub-group analyses were considered to be relevant. This is consistent with clinical advice given to the ERG that is noted on page 105: *"The populations in the clinical trials were broadly similar to those seen in UK clinical practice."* And page 107: *"The patient populations in the economic model appropriately reflect the licensed indications for apalutamide and the clinical trial populations."*	*UK clinical experts stated that the characteristics of mHSPC patients in the TITAN trial were broadly reflective of patients in UK clinical practice."*		

Issue 12 Adjustment for crossover and novel therapies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 109 of the ERG report it states: *"As shown in the table, the estimates from TITAN were not adjusted: adjustment for novel therapy was explored but not included in the cost-effectiveness analysis because the proportion of patients who had more than one novel therapy was relatively low."*	The proposed amendment is to change the wording to: *"As shown in the table, the estimates from TITAN were not adjusted: adjustment for novel therapy was explored but not included in the cost-effectiveness analysis because the adjusted analysis failed to demonstrate any significant impact on survival outcomes and gave counter-*	The rationale outlined in section B.3.3.2.2 has not been accurately reported.	The text has been amended (see page 109).

However, this does not capture the true rationale for not including this approach in the cost-effectiveness analysis.	*intuitive results in some scenarios."*		

Issue 13 Extrapolation of MFS and rPFS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 122 of the ERG report it states: *"We note, however, that the PH assumption does not seem to be supported by the trial data and, therefore, Weibull may not be the most appropriate statistical distribution to model rPFS."* A similar statement is made on page 115 with regards to MFS. This statement is inaccurate as an independently fitted Weibull model does not assume proportional hazards.	These statements should be deleted as they are mis-leading.	An independently fitted Weibull model does not assume proportional hazards as both the shape and scale of the curve can vary. Instead, the Weibull assumes the hazard function can either increase or decrease monotonically. Given the statement in the ERG report is inaccurate and because it is stated elsewhere that the ERG agreed with the use of the Weibull curve in the base-case analysis, we propose these statements are deleted.	The statements on pages 115 and 122 have been deleted.

Issue 14 Overall survival for nmHRPC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 118 of the ERG report it states:	The proposed amendment is to change the wording to:	The rationale provided in the ERG report does not fully reflect the	This is not a factual error. However, this statement and the ERG conclusions on page 118

"The company concluded that, given the limited number of historical ADT OS data available from literature, the 'informed fits' approach was thought to provide only minimal additional benefit and, therefore, was not used in the analysis." This does not fully capture the justification provided in the company submission.	*"The company concluded that given the limited amount of historical ADT OS data available from the literature and the fact that SPARTAN had longer follow-up than all of these studies, the informed fits approach provided no additional benefit and, and therefore was not carried through into the modelling.*	justification provided in Section B.3.3.2.3 of the company submission.	have been amended to provide more clarity.

Issue 15 mHSPC historical OS data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 127 of the ERG report it states: *"We note, however, that based on feedback from the advisory board, current patients in clinical practice would perform better than patients from the historical ADT arm. Therefore, using the historical ADT arm in the economic analysis is likely to increase uncertainty in the economic outcomes."* However, the informed fits approach accounts for any differences in the scale of outcomes between the TITAN trial and the historical data, and therefore addresses this	The proposed amendment is to change the wording to: *"We note, however, that based on feedback from the advisory board, current patients in clinical practice would perform better than patients from the historical ADT arm. However, although the historical ADT arm may not completely reflect outcomes in practice today, the informed fits approach adjusts for differences between these data and the TITAN trial."*	The informed fits analysis uses external data with a longer follow-up period and includes it as a third treatment arm in order to inform extrapolations (i.e. apalutamide plus ADT based on TITAN trial, ADT alone based on TITAN trial, and a third arm based on ADT-pooled). The third arm used in the informed fits approach consists of the ADT-pooled arm. The underlying assumption of this method is that the shape parameter of any parametric distribution is a study independent parameter and could be used from external data to inform the shape of the new clinical trial. This assumption was visually assessed with a log-cumulative hazards plot and statistically tested with a Schoenfeld test which demonstrated the assumption holds.	This is not a factual error and, therefore, no amendments have been made. Moreover, as stated on page 127 of the ERG report, "the implementation and the outcomes of the 'informed fits' approach could not be verified because the IPD were not made available to the ERG".

uncertainty.		Therefore, this approach accounts for differences between the historical data and the TITAN trial, and therefore although this historical ADT data is not completely reflective of clinical practice today, this is reflected in the analysis.	

Issue 16 Application of adverse event disutilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 135 of the ERG report it states: *"We consider that the adverse event disutility is overestimated for the mHSPC/nmHRPC health states as in the model when patients suffer an AE, a disutility for these patients is then applied for the remainder of that health state. However, Aes mostly only last for up to two weeks (CS Table 64). We have made this change for the adverse events in the ERG base case."* However, this is not consistent with how the adverse event coefficient in the utility regression analysis was coded.	This statement and scenario analysis should be removed as it does not accurately reflect how the adverse event disutilities were estimated.	As outlined in Section B.3.4.5 of the company submission, the adverse event coefficients in the SPARTAN and TITAN utility regressions were coded as "0" before a patient experienced an adverse event and "1" from that point onwards. This means that every EQ-5D questionnaire that was completed at any point following a reported adverse event was classed as an adverse event observation. Therefore, the coefficient was multiplied in each model cycle by the proportion of patients assumed to have experienced an AE by each time point. The ERG are correct that most adverse events will likely only impact utility for a couple of weeks, but the company's approach does not contradict this. The analysis captures the difference between the utility of patients who did experience an adverse event during the trials and those who did not. Therefore, the ERG's approach of applying the disutility only for the assumed duration of an adverse event is	We thank the company for added clarification on this issue. However we do not consider this issue is a factual error and our view on this matter remains as stated.

		not appropriate as it is not consistent with how the analysis was coded. We would expect that the size of the disutility itself would be greater had we only look for questionnaires at the same time an AE was being experienced (however there would be considerably less observations for analysis).	

Issue 17 Validation of post-progression survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 147 of the ERG report it states: *"The ERG considers that comparing the life-years spent in the mHRPC health states of the model directly against the previous NICE appraisals' post-progression survival results would be more reasonable than adjusting the model life-years for the proportion of patients who progress. Therefore, we update CS Table 98, without the adjustment, as part of the ERG's model validation."* However, this is not appropriate at the post-progression estimates from the model are not equivalent to what is reported in the previous mHRPC submissions	This statement should be removed as well as the comparisons made between the unadjusted post-progression estimates from the model and the estimates from previous submissions.	The survival estimates from previous submissions in mHRPC present the mean survival times from the point at which patients are classed as having mHRPC. However, the post-progression survival times in the model capture the average time spent in post-progression survival from the mHSPC or nmHRPC health states. This includes the impacts of deaths pre-progression (patients will have 0 time spent in post-progression survival in this case). Patients who died pre-progression clearly are not present in the published mHRPC models. Therefore, these values are not using the same baseline timepoint and are not comparable. An adjustment is required to ensure we capture the average post-progression survival time of patients who did not die prior to disease progression. This ensures that the values from the previous submissions in mHRPC and the cost-	This is not a factual error and reflects a difference of opinion on how the model results should be validated against previous submissions.

		effectiveness model are consistent.	

References

1. Aly A, Mullins CD and Hussain A. Understanding heterogeneity of treatment effect in prostate cancer. *Curr Opin Oncol*. 2015; 27(3):209-16.
2. National Institute for Health and Care Excellence (NICE). TA377: Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. 2016. Available at: https://www.nice.org.uk/guidance/ta377. Accessed: 08 December 2017.
3. National Institute for Health and Care Excellence (NICE). TA580: Enzalutamide for hormone-relapsed non-metastatic prostate cancer. 2019. Available at: https://www.nice.org.uk/guidance/ta580. Accessed: 05 August 2019.
4. National Institute for Health and Care Excellence (NICE). TA387: Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. 2016. Available at: https://www.nice.org.uk/guidance/ta387. Accessed: 08 December 2017.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Apalutamide for treating prostate cancer [ID1534]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments: **4 January 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, 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 engagement 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.

About you

Your name	**Nicola Trevor**
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**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: selection of methods to adjust for treatment switching in the pivotal apalutamide clinical trials (nmHRPC and mHSPC)	**Yes**	**1. Treatment switching adjustment for SPARTAN and TITAN** **1.1. Background** In SPARTAN and TITAN, patients in the androgen deprivation therapy (ADT) plus placebo arm of each trial could switch over to the apalutamide plus ADT arm when the trials were unblinded at the time of the first interim analyses. This crossover could potentially improve outcomes for patients in the placebo plus ADT arm, leading to an underestimation of the relative benefit for apalutamide plus ADT versus placebo plus ADT on secondary progression-free survival (PFS2) and overall survival (OS). Additionally, following disease progression to the metastatic hormone relapsed prostate cancer (mHRPC) disease state, patients in both arms in SPARTAN and TITAN could receive the novel therapies abiraterone and enzalutamide as subsequent treatment options. Consequently, some patients in each arm of each trial received more than one novel therapy. In UK clinical practice, only one novel therapy is permitted in the prostate cancer treatment pathway. As this exposure to a second novel therapy occurred more in the active arm (apalutamide being a novel therapy), PFS2 and OS may be overestimated in

		favour of the apalutamide plus ADT arm, which may lead to the overestimation of the relative treatment effect. All statistical methods, as recommended in the NICE decision support unit (DSU) technical support document (TSD) 16,[(1)] were considered to render the PFS2 and OS outcomes more generalisable to UK clinical practice, by adjusting simultaneously for treatment crossover as well as for the one novel therapy restriction. Three of the four methods recommended in DSU TSD 16 were not viable to adjust SPARTAN or TITAN data. These were the rank preserving structural failure time model (RPSFTM), iterative parameter estimation (IPE) and two-stage method. Full explanation of why these methods were not viable is given in Appendix R of Document B of Janssen's submission. To summarise, RPSFTM and IPE were not viable due to insufficient data available in SPARTAN and TITAN to reliably estimate the multiple parameters required. The two-stage method was not viable due to the above and the requirement for a secondary baseline at time of switching (see Figure 84/Figure 85 and Figure 92/Figure 93 in Appendix R of Document B of Janssen's submission). As detailed in Janssen's submission a modified version of the RPSFTM and the inverse probability of censoring weights (IPCW) methods were explored to adjust SPARTAN and TITAN (see Appendix R of Document B of Janssen's submission). Since the original submission, a new data cut became available for TITAN. The clinical cut-off date was 7th of September 2020 after a median duration of follow up of [redacted] months. More details are provided in Section 7 of this document. Following the questions raised in the Evidence Review Group (ERG) report

on the modified RPSFTM and IPCW methods and the availability of additional data from the final analysis of TITAN, additional information is presented in this section.

A summary of the methods previously presented in Appendix R of Document B as well as the new analyses added for this technical engagement response document, are summarised in Table 1 for SPARTAN and Table 2 for TITAN.

Table 1. Summary of survival adjustment methods used for SPARTAN

Submission document	Method	Rationale
Appendix R for document B	RPSFTM without recensoring	Used external data from COU-AA-302 FA to overcome limitations of using only SPARTAN data to calculate parameters
	RPSFTM with recensoring	Used external data from COU-AA-302 FA to overcome limitations of using only SPARTAN data to calculate parameters
Janssen Technical engagement responses (this document)	IPCW	To present the results initially not included in Appendix R (due to their counterintuitive nature), in response to a request in the ERG report for results from a range of methods to be presented
	RPSFTM without recensoring	Using COU-AA-302 IA3 data as sensitivity analysis (minimal crossover at IA3) to test the impact of crossover in this trial.
	RPSFTM with recensoring	Using COU-AA-302 IA3 data as sensitivity analysis (minimal crossover at IA3) to test the impact of crossover in this trial

Abbreviations: FA: final analysis; IA3: third interim analysis; IPCW: inverse probability of censoring weights; RPSFTM: rank preserving structural failure time model

Table 2. Summary of survival adjustment methods used for TITAN

Submission document	Method	Rationale
Appendix R for document B	IPCW	Alternative approach to implement survival adjustment
	RPSFTM without recensoring	Used external data from COU-AA-302 FA to overcome limitations of using only TITAN data to calculate parameters
	RPSFTM with recensoring	Used external data from COU-AA-302 FA to overcome limitations of using only TITAN data to calculate parameters
Janssen Technical engagement responses (this document)	IPCW	Update with TITAN FA data
	RPSFTM without recensoring	Update with TITAN FA data and to use COU-AA-302 IA3 data as sensitivity analysis (minimal crossover at IA3)
	RPSFTM with recensoring	Update with TITAN FA data and to use COU-AA-302 IA3 data as sensitivity analysis (minimal crossover at IA3)

Abbreviations: FA: final analysis; IA3: third interim analysis; IPCW: inverse probability of censoring weights; RPSFTM: rank preserving structural failure time model

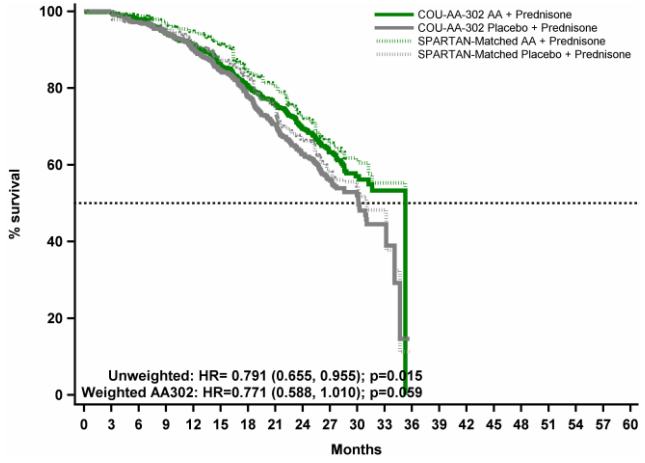
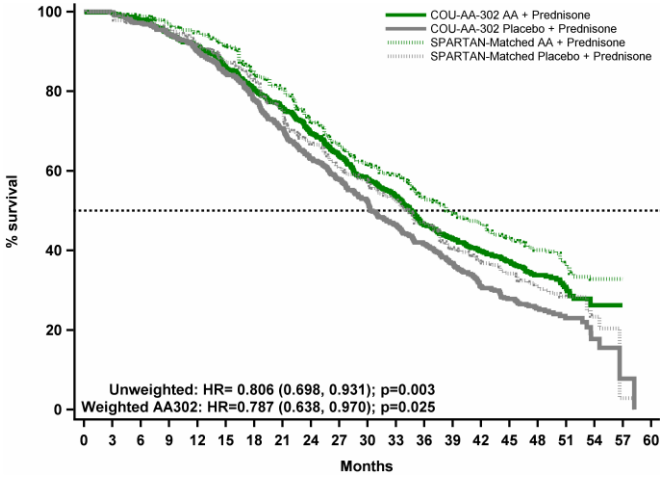
1.2. RPSFTM (modified)

		RPSFTM reconstructs the counterfactual survival time of patients who switched to a non-permitted therapy, in this case either due to crossover from the placebo to the apalutamide arm or due to receiving a second novel therapy. The main assumption behind RPSFTM is that of common treatment effect, which assumes that the benefit of the treatment (in this case apalutamide plus ADT) is equal in patients exposed to it at a later timepoint as in those randomised to it at baseline. The RPSFTM is typically applied in a setting with a simple switching pattern, with patients switching from the control arm to the active arm, where only the relative treatment effect of one active therapy vs control needs to be estimated based on the trial data. This would be suitable if we only need to adjust for treatment cross-over. In a setting that involves crossover as well as patients receiving a second novel therapy, patients are switching to more than one active therapy, each with a specific relative treatment effect versus placebo. Multiple parameters need to be estimated, that is separate estimates for apalutamide and for other second novel treatments, even when assuming similar efficacy for all these second novel treatments. In this case, data available in the trial are not sufficient to allow for the reliable estimation of the multiple parameters.(1) To overcome the limitations of RPSFTM described in the preceding paragraph, on the need to estimate multiple parameters, an alternative method is used.(2) Conceptually similar to RPSFTM, the alternative method (referred to in the ERG report as 'modified RPSFTM') avoids the need for multi-parameter

		estimation within the trial, by borrowing randomised evidence external to SPARTAN and TITAN to estimate the treatment effect related to the second subsequent novel therapy to be adjusted for. In the 'modified RPSFTM', patient level data from COU-AA-302, a randomised clinical trial comparing abiraterone acetate plus prednisone versus placebo plus prednisone in patients with mHRPC, is used to estimate (and adjust for) the survival benefit attributed to a second novel therapy in SPARTAN and TITAN. After progression (post metastasis in SPARTAN, post radiographic progression in TITAN), patients from both trials became mHRPC patients, similar to the patients in COU-AA-302. As no similar trial data were available for enzalutamide, similar efficacy was assumed for enzalutamide and abiraterone in mHRPC, which may be only a minor limitation to the analysis, as abiraterone was the most and second most commonly initiated subsequent novel therapy in SPARTAN and TITAN respectively. The shrinkage factor based on the acceleration factor (AF) resulting from an accelerated failure time (AFT) model applied to data from COU-AA-302 was used to derive counterfactual survival times adjusted for second use of a novel therapy (abiraterone/enzalutamide) in both trial arms of SPARTAN and TITAN. **RPSFTM adjustment for SPARTAN** ***COU-AA-302 data weighting*** The estimation of the survival benefits of abiraterone acetate using AFT-modelling in the COU-AA-302 trial was conducted on data from two of the trial's data cuts; interim analysis 3 (IA3) and final analysis (FA). This was done to address concerns raised by the ERG that survival benefit of abiraterone in COU-AA-302 may be biased as patients in the placebo arm of the trial were permitted to cross-over to the

		abiraterone arm at unblinding. Results from COU-AA-302 show that, while the FA datacut may be affected by crossover, the impact should be minimal for the IA3 data cut as only 3 patients (0.55% of the 542 originally randomised to the prednisone alone arm) had crossed-over at this stage.[3] Thus, the IA3 data was implemented to provide a sensitivity analysis. This sensitivity analysis could only be conducted for OS as PFS2 data was not available for IA3. Though both COU-AA-302-patients and progressed patients from SPARTAN have metastatic hormone resistant prostate cancer, these populations may still differ on other characteristics, which may impact the relative treatment effect (treatment effect modifiers). To adjust for these differences, a propensity score-based inverse probability weights (IPW) approach was applied to the COU-AA-302 patient population to match the characteristics of the subgroup of SPARTAN patients having abiraterone and enzalutamide (whichever was given first) as subsequent therapies. The updated baseline for SPARTAN is at the time of switch to abiraterone/enzalutamide. The resulting propensity scores were used to derive the inverse probability weights (ATT weights) for the COU-AA-302 population to reflect the characteristics of the SPARTAN switching population. Unweighted and weighted OS KM curves for the COU-AA-302 trial are displayed in Figure 1A (IA3) and Figure 1B (FA). In both cases, weighted OS curves shift up equally (i.e. better absolute OS) in both arms compared to intention to treat (ITT), suggesting mHRPC patients from SPARTAN are less severe compared to the COU-AA-302-patients. However, the impact of weighting on the relative treatment effect was minimal: the estimated AF derived from weighted COU-AA-302 was 0.86 (versus 0.87 without IPW) for the FA data cut and 0.89 (versus 0.89 without IPW) for the IA3 data cut.

Figure 1: OS KM and estimation of shrinkage factor for abiraterone: (COU-AA-302)

A. COU-AA-IA3	B. COU-AA-FA
	

Abbreviations: AA: abiraterone acetate; HR: hazard ratio; IA3: interim analysis 3; ITT: intention to treat; KM: Kaplan Meier; FA: final analysis; OS: overall survival

OS and PFS2 RPSFTM results for SPARTAN

Results for the adjustment of OS in SPARTAN are shown in Table 3 (utilising final analysis data for COU-AA-302 in RPSFTM) and Table 4 (utilising IA3 data for COU-AA-302 in RPSFTM).

The OS hazard ratio (HR) generated from RPSFTM without re-censoring using FA data for COU-AA-302 (HR = [redacted]; 95% confidence interval [CI], [redacted]; [redacted]) was selected as the base case.

The HR from the sensitivity analysis conducted using RPSFTM without re-censoring and IA3 data for COU-AA-302 (HR =0.773; 95% CI, 0.634; 0.942) is similar to the base case HR. This illustrates the limited impact of cross-over in the COU-AA-302 trial on the results. As discussed earlier, whilst 93 patients had crossed over from the placebo arm to the abiraterone arm by the time of final analysis, only 3 had done so at the time of IA3. [3, 4]

Table 3. Comparison of OS hazard ratios of apalutamide versus placebo in SPARTAN FA following RPSFTM adjustment. exp(ψ^{ST}) is estimated from COU-AA-302 FA

Method	exp(ψ^{ST}) [a]	exp(ψ^{a})	SPARTAN HR (95% CI)
ITT			[redacted]
RPSFTM without recensoring	0.86	0.81	[redacted]
RPSFTM with recensoring	0.86	0.76	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat; OS: overall survival; RPSFTM: rank preserving structural failure time model
Notes: [a] Estimated from the weighted (Spartan-Matched) AA302 dataset

Table 4. Comparison of OS hazard ratios of apalutamide versus placebo in SPARTAN FA following RPSFTM adjustment. exp(ψ^{ST}) is estimated from COU-AA-302 IA3

Method	exp(ψ^{ST}) [a]	exp(ψ^{a})	SPARTAN HR (95% CI)
ITT			[redacted]
RPSFTM without recensoring	0.89	0.83	[redacted]
RPSFTM with recensoring	0.89	0.77	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; IA3: third interim analysis; ITT: intention-to-treat; OS: overall survival; RPSFTM: rank preserving structural failure time model
Notes: [a] Estimated from the weighted (Spartan-Matched) AA302 dataset

The RPSFTM adjusted HRs for PFS2 in the SPARTAN trial are presented in Table 5, using the final analysis data cut for COU-AA-302.

Table 5. Comparison of PFS2 hazard ratios of apalutamide versus placebo in SPARTAN following RPSFTM adjustment. exp(ψ^{ST}) is estimated from COU-AA-302 (Final analysis)

Method	exp(ψ^{ST}) [a]	exp(ψ^{a})	SPARTAN HR (95% CI)
ITT			[redacted]
RPSFTM without recensoring	0.49	0.57	[redacted]
RPSFTM with recensoring	0.49	0.48	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; ITT, intention-to-treat; PFS2, second progression-free survival; RPSFTM: rank preserving structural failure time model
Notes: [a] Estimated from the weighted (Spartan-Matched) AA302 dataset

Recensoring

RPSFTM HRs without recensoring were selected for the base case for OS and PFS2. These were selected over the 'with re-censoring' HRs as the latter method is considered to underestimate control-group mean survival therefore overestimating the treatment effect for apalutamide plus ADT.

Re-censoring often involves a loss of longer term survival information, which is problematic when estimates of long term survival effects are required.[5] This was an issue in SPARTAN where re-censoring resulted in a considerable shortening of the adjusted Kaplan-Meier (KM) curve especially for PFS2.

OS and PFS2 RPSFTM results for TITAN final analysis

Details of the switching patterns for TITAN FA are presented in Appendix C of this report.

The 'modified RPSFTM' method informed by external data from the COU-AA-302 trial was applied to TITAN data in the same way as that described above for SPARTAN.

The RPSFTM generated OS HR displayed in Table 6 using the final analysis data cut for COU-AA-302, are very similar to those displayed in Table 7 using the IA3 data cut for COU-AA-302. This again demonstrates the limited impact of crossover in the COU-AA-302. The same as with the previous datacut, adjusted HRs (with and without recensoring) predict a greater treatment benefit for apalutamide following adjustment. To align with the method selected for the base case in the original submission and because this approach produces a conservative estimate of the treatment effect, the unadjusted OS curves were implemented as the base case in the economic model.

Table 6. Comparison of OS hazard ratios of apalutamide versus placebo in TITAN FA following RPSFTM adjustment. exp(ψ^{ST}) is estimated from COU-AA-302 FA

Method	exp(ψ^{ST}) [a]	exp(ψ^{a})	TITAN HR (95% CI)
ITT			[redacted]
RPSFTM without recensoring	0.89	0.67	[redacted]
RPSFTM with recensoring	0.89	0.65	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; overall survival; RPSFTM: rank preserving structural failure time model
Notes: [a] Estimated from the weighted (Titan-Matched) AA302 dataset

Table 7. Comparison of OS hazard ratios of apalutamide versus placebo in TITAN FA following RPSFTM adjustment. exp(ψ^{ST}) is estimated from COU-AA-302 IA3

Method	exp(ψ^{ST}) [a]	exp(ψ^{a})	TITAN HR (95% CI)
ITT			[redacted]
RPSFTM without recensoring	0.91	0.67	[redacted]

RPSFTM with recensoring	0.91	0.66	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; IA3: third interim analysis; OS: overall survival; RPSFTM: rank preserving structural failure time model
Notes: [a] Estimated from the weighted (Titan-Matched) AA302 dataset

The RPSFTM generated PFS2 HR using the final analysis data cut for COU-AA-302 is displayed in Table 8. The same with the previous TITAN datacut the unadjusted HR; [redacted], 95% CI ([redacted]) was selected for the base case as a conservative estimate of the treatment effect over the HRs generated via RPSFTM with recensoring. Note that this unadjusted HR was derived using different censoring rules to those specified in the TITAN protocol, See Appendix C for rationale and details.

Table 8. Comparison of PFS2 hazard ratios of apalutamide versus placebo in TITAN FA following RPSFTM adjustment. exp(ψ^{ST}) is estimated from COU-AA-302 FA

Method	exp(ψ^{ST}) [a]	exp(ψ^{a})	TITAN HR (95% CI)
ITT[b]			[redacted]
RPSFTM without recensoring	0.54	0.62	[redacted]
RPSFTM with recensoring	0.54	0.59	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; ITT, intention-to-treat; PFS2, second progression-free survival; RPSFTM: rank preserving structural failure time model.
Notes: [a] Estimated from the weighted (Titan-Matched) AA302 dataset; [b] including deaths after switching to 2nd subsequent treatment

1.3. IPCW adjustment for SPARTAN and TITAN

The methods used to implement the IPCW adjustment are described in detail in Appendix R of Document B in the original company submission.

		In summary, IPCW is a model-based method that reweights patients using inverse probability weighting method as detailed below. Patients are artificially censored at the time of switch. • To compensate for selection bias induced by this artificial censoring, the patients still on the original treatment were reweighted over time by the inverse of their time-dependent probability to stay on treatment, in order to represent similar patients who were already censored before. These time-dependent stabilized weights are calculated using repeated logistic regression, modelling the probability to stay on treatment at any time interval. The denominator of the stabilized weights is obtained by including baseline and time-varying covariates in the model, while only baseline covariates are included for the numerator. A stepwise selection process, at 0.15 level, was employed to identify a subset of baseline and time-varying covariates that can predict the probability of not switching. This step was done for each trial arm separately. • IPCW-adjusted HR for OS was calculated using a Cox proportional hazards model, including the time-dependent weights and baseline characteristics. • Weighted placebo KM curve based on stabilised weights was generated using the formula provided by Howe et al., 2011.[6] The IPCW method assumes no unmeasured confounders related to both baseline and time-dependent patient characteristics; although this assumption cannot be tested, most clinically relevant prognostic factors available in the trial were included in the statistical modelling. The method is likely to work adequately if the assumption is approximately true, and no important independent predictors are missing. **IPCW Results for SPARTAN**

		As shown in Figure 2 and Figure 3 for OS and PFS2 respectively, IPCW and naïve censoring KM curves are very close, implying that selection bias induced by the censoring at time of initiation of subsequent therapy to be adjusted for, was not corrected for by the second step. **Figure 2. OS KM curves, unadjusted and adjusted using IPCW: SPARTAN**  **Abbreviations:** APA: apalutamide IPCW: inverse proportion of censoring weights; ITT: intention to treat; KM: Kaplan Meier; OS: overall survival

Figure 3. PFS2 KM curves, unadjusted and adjusted using IPCW: SPARTAN

Abbreviations: APA: apalutamide IPCW: inverse proportion of censoring weights; ITT: intention to treat; KM: Kaplan Meier; PFS2, second progression-free survival

The OS HR generated using the IPCW (HR = [redacted]; 95% CI, [redacted];[redacted]), Table 9, was considered clinically implausible as it showed counterintuitive results which suggest an even larger relative treatment effect for apalutamide plus ADT versus placebo plus ADT following adjustment, and imply that receiving subsequent therapy is harmful to patients. The PFS2 generated using IPCW (Table 10) was also considered implausible for the same reason.

The results illustrate that the time dependent weighting applied as the second step in the IPCW method was not able to adjust for the considerable selection bias induced by the naïve censoring in the first step.

Table 9. Comparison of OS hazard ratios of apalutamide versus placebo following IPCW adjustment in SPARTAN

Method	SPARTAN HR (95% CI)
ITT	[redacted]
IPCW	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; IPCW: inverse probability of censoring weights; ITT: intention-to-treat; OS: overall survival

Table 10. Comparison of PFS2 hazard ratios of apalutamide versus placebo following IPCW adjustment in SPARTAN

Method	SPARTAN HR (95% CI)
ITT	[redacted]
IPCW	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; IPCW: inverse probability of censoring weights; ITT, intention-to-treat; PFS2, second progression-free survival

IPCW results for TITAN updated data-cut

Unadjusted and IPCW adjusted OS and PFS2 curves for TITAN are shown in Figure 4 and Figure 5. Similar to SPARTAN, IPCW and naïve censoring KM curves are very close, implying that selection bias induced by the censoring at time of initiation of subsequent therapy to be adjusted for, was not corrected for by the second step. The available time-varying covariates cannot predict well the switching in the

		apalutamide plus ADT arm and provide insufficient weights to compensate for the selection bias induced by the naïve censoring step. **Figure 4. OS KM curves, unadjusted and adjusted using IPCW: TITAN FA**  **Abbreviations:** APA: apalutamide IPCW: inverse proportion of censoring weights; ITT: intention to treat; KM: Kaplan Meier; OS: overall survival

Figure 5. PFS2 KM curves, unadjusted and adjusted using IPCW: TITAN FA

Abbreviations: APA: apalutamide IPCW: inverse proportion of censoring weights; ITT: intention to treat; KM: Kaplan Meier; PFS2, second progression-free survival

The IPCW adjusted HRs for OS and PFS2 for TITAN are displayed in Table 11 and Table 12 respectively alongside the unadjusted HRs for comparison. In both cases, the IPCW adjusted HRs were deemed clinically implausible. As with SPARTAN, the results illustrate that the time dependent weighting applied as the second step in the IPCW method was not able to adjust for the considerable selection bias induced by the naïve censoring in the first step.

Table 11. Comparison of OS hazard ratios of apalutamide versus placebo following IPCW adjustment in TITAN

Method	TITAN HR (95% CI)
ITT	[redacted]
IPCW	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; IA3: third interim analysis; IPCW: inverse probability of censoring weights; OS: overall survival

Table 12. Comparison of PFS2 hazard ratios of apalutamide versus placebo following IPCW adjustment in TITAN

Method	TITAN HR (95% CI)
ITT[a]	[redacted]
IPCW	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; IPCW: inverse probability of censoring weights; ITT, intention-to-treat; PFS2, second progression-free survival
Notes: [a], including deaths after switching to 2nd subsequent treatment

Reasons for not selecting IPCW for SPARTAN and TITAN

IPCW can provide unbiased estimates of the relative treatment effect if all baseline and time-varying covariates (influencing switching in each arm and survival) are available and can be adjusted for.

		Reliability of IPCW therefore depends on the availability of the relevant baseline and time-varying covariates driving the treatment switching and the availability of a sufficient number of (and sufficiently similar) patients continuing on treatment to represent the censored patients. On the contrary, IPCW may become unreliable when the proportion of patients switching is high and/or switching patients may be too different from non-switching patients. The objective is to estimate counterfactual survival curves for a trial where exposure to a second novel therapy would not have been allowed, according to UK rules. Assuming that treatment with a second novel therapy has a positive impact on outcomes, the counterfactual survival curves are expected to be below the observed survival curves, representing worse outcome (and as discussed above, especially for the active arm, as more patients were exposed to second novel therapy). IPCW results in the current analyses for both OS and PFS2, however, show the opposite change, with counterfactual survival curves for the apalutamide arm moving upwards, suggesting that if these patients would not have been exposed to second novel therapy, their outcomes on OS and PFS2 would have been better. This would imply that exposure to second novel therapy would be harmful, which is not clinically plausible. These results illustrate that in the current case the assumptions behind IPCW (related to full adjustment for selection bias induced by artificially censoring patients at time of switch to the second novel therapy) are not fulfilled. In SPARTAN, the artificial censoring (as a first step in IPCW) leaves out a high number of death events (n= 183 out of 274) and PFS2 events (n=209 out of 319) in the apalutamide arm (shifting survival curves upwards), which is not compensated for by the inverse probability based reweighting process: the derived IPC weights are not able to correct for the selection bias introduced by the artificial censoring at the time of switch. In TITAN, although, fewer death/PFS2 events were censored in both

		arms, there was insufficient data (in terms of baseline or time-varying characteristics) to accurately predict the UK switching mechanism, especially in the apalutamide arm. Hence, the apalutamide arm also provides a clinically implausible adjusted KM curve, which still lies above the ITT KM curve. ***Summary*** By providing the detail above, Janssen aim to address the concerns raised in the ERG Report relating to: 1. Selection of methods used to adjust for crossover and treatment switching 2. Bias in the selected method 3. Impact on cost-effectiveness results As noted above, 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 (RPSFTM, IPE, two-stage) or produced clinically implausible results (IPCW). As such, the modified RPSFTM approach, using external data to improve reliability of the method, was employed. Although, this method is not free from bias, the results produced were at least clinically plausible. Within this method, potential bias arising from crossover in the external data (COU-AA-302) used has been explored, with results indicated any bias is minimal. It is important to note, however, that the common treatment 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.

		Only methods producing clinical effectiveness estimates less favourable than those observed in SPARTAN and TITAN have been taken forward into the economic modelling. The reason for this is to ensure a conservative approach to cost-effectiveness is taken and that Appraisal Committee time is optimised by focus on clinically plausible scenarios.
Key issue 2: clinical and cost effectiveness of apalutamide in people with mHSPC who are eligible or unsuitable for docetaxel chemotherapy	**Yes**	**2. Clinical and cost-effectiveness of apalutamide in people with mHSPC who are ineligible or unsuitable for docetaxel chemotherapy** The ERG raises two concerns with respect to the subgroup of metastatic hormone sensitive prostate cancer (mHSPC) patients who are ineligible or unsuitable for docetaxel chemotherapy. The first being the identification of these patients and the second being the generalisability of results from TITAN to these patients. These are understandable concerns, that have also been present in the ongoing appraisal (ID945) of abiraterone in mHSPC (high risk). Indeed, these concerns were explored at length in the successful appeal for ID945 and subsequent Appraisal Committee meeting on the 10th December 2020. At the time of writing, the outcome of the Appraisal Committee's reconsideration of these two concerns is not yet known with respect to abiraterone. Much can be understood, however, from the discussions pertaining to abiraterone that is relevant to the appraisal of apalutamide. It is important to note two key points in relation to these concerns. Firstly, the unmet need for an effective treatment in patients ineligible/unsuitable for chemotherapy is substantial. The National Prostate Cancer Audit (NPCA) conducted prior to the COVID-19 pandemic found that only 27% of mHSPC patients received docetaxel.(7) This figure is likely to be an underestimate as docetaxel usage was restricted further as a result of COVID-19. And so currently, at least three-

		quarters of patients with mHSPC are ineligible or unsuitable for chemotherapy. These patients, only option is to remain sub-optimally treated with ADT alone until the inevitable progression to mHRPC, at which point alternative anti-cancer therapies are available. Secondly, chemotherapy ineligible/unsuitable patients represent the majority of mHSPC patients. As such, the generalisability of the TITAN trial 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. **2.1. Identifying chemo-unsuitable or ineligible patients** A patient's eligibility for receiving chemotherapy is multi-factorial and extends beyond just contraindications to docetaxel. Chemo-ineligible/unsuitable patients include those who are unsuitable for chemotherapy due to frailty and comorbidities, location of treatment centers, ease of access to treatment, alongside social and emotional state and presence of a carer etc. Criteria to identify patients who are unsuitable for chemotherapy have been described in the following two documents which serve to highlight the importance of exercising clinical judgement in making decisions regarding patients' eligibility or suitability for docetaxel. **TA412**

		When appraising Radium 223 in TA412 for patients with metastatic hormone-relapsed-prostate cancer (mHRPC), NICE accepted that clinical criteria could be used to define the group of patients who could not have docetaxel.[8] Excerpts from the guidance read: *"The committee heard from clinical experts that there are people for whom docetaxel is contraindicated or unsuitable, and who would typically have best supportive care in clinical practice. The clinical expects stated that this group of people could be considered for treatment with radium-223. However, they emphasised that people in this group are difficult to define and that making such a treatment decision needed an assessment of multiple factors such as age, wellbeing and co-morbidities. The committee accepted the views of the clinical experts that there is a clinically recognised group for whom radium-223 treatment is suitable, because docetaxel is contraindicated or unsuitable. It concluded that, for this group of people, best supportive care is the most relevant comparator."* Paragraph 4.31 of the FAD for TA412 sets out the criteria for defining the people for whom docetaxel is not suitable:[8] • contraindications to docetaxel such as hypersensitivity to the active substance, a neutrophil count of less than 1.5x109/litre, or severe liver impairment • a platelet count of less than 100x109/litre • ongoing treatment with an immunosuppressant for any condition • an ECOG performance status of 3 or greater • comorbidities and an ECOG performance status of 2 or greater • comorbidities, including: ○ poor cognition or social support, which results in inability to understand treatment and provide consent

		Blueteq criteria Blueteq is a system used by NHS England to ensure that access to certain medicines is limited to appropriate patients. The system operates by requiring prescribers to complete a questionnaire for relevant patients before funding of treatment is approved. At the third meeting of the Appraisal Committee for ID945, NHS England proposed Blueteq criteria for abiraterone for chemo-ineligible/unsuitable patients with newly diagnosed, high risk, mHSPC. The questions to be answered by a prescriber prior to prescription of abiraterone were as follows: *"I confirm that I have assessed this patient's eligibility for receiving upfront docetaxel plus ADT and have concluded that the patient **cannot** or **should not** or has **chosen not** to be treated with docetaxel.* *Please mark below which of these 3 clinical scenarios apply to this patient:* • *the patient commenced docetaxel and has had to discontinue docetaxel within 2 cycles of its start on account of life-threatening toxicity (i.e. **the patient CANNOT receive docetaxel**)* • *the patient has significant comorbidities which preclude treatment with docetaxel (i.e. **the patient SHOULD NOT be treated with docetaxel**) and this has been fully discussed with the patient. It is recommended that validated systems of scoring clinical frailty are used as part of the oncology assessment as to explaining the benefits and risks of chemotherapy and abiraterone* • *the patient has been fully consented regarding the advantages and disadvantages of both upfront docetaxel chemotherapy and abiraterone and also that use of upfront abiraterone would result in there being no further possible treatment with any androgen receptor targeted agents when the patient's disease progresses and that the patient may not be fit enough to receive docetaxel when the patient's disease progresses. After such informed consent, the patient has chosen to receive upfront abiraterone (i.e. **the patient has CHOSEN NOT to be treated with docetaxel**)."*

		As noted above, reconsideration of whether it is possible to identify chemo-ineligible/unsuitable patients in mHSPC occurred at the post-appeal Appraisal Committee meeting for ID945. Although, the outcome of this reconsideration is not yet known, it is expected that criteria to identify such patients will be included within the guidance for ID945. Should an optimised recommendation for apalutamide be necessary it would seem appropriate to use these criteria to identify chemo-ineligible/unsuitable patients for the purposes of guidance. **2.2. Effectiveness of apalutamide in patients who are unsuitable or ineligible for chemotherapy** As noted above, chemo-ineligible/unsuitable patients represent the majority of mHSPC patients. As such, the efficacy results for apalutamide from TITAN can reasonably be considered no less generalisable than most oncology trials. Moreover, eligibility/suitability for chemotherapy was not a pre-specified criterion in TITAN and clinicians could not determine what proportion of the trial population may be chemo-ineligible in practice when reviewing patients' baseline characteristics. However, clinical experts consulted by Janssen stated that there would be a proportion of patients in clinical practice who currently only receive ADT, due to ineligibility for chemotherapy or location of treatment centres and ease of access to treatment. The clinicians agreed that they would be happy to prescribe apalutamide to these patients on the basis of results from TITAN .[(9)] Apalutamide plus ADT demonstrated a consistent treatment effect in terms of OS across all prespecified subgroups as shown in Figure 6. Of note, the interaction effects assessment for Age and Eastern Cooperative Oncology Group (ECOG) performance status were both non-significant, demonstrating that

		these two characteristics were not treatment effect modifiers for apalutamide. This provides evidence that the TITAN trial is applicable to all mHSPC patients, including older patients and those with higher ECOG - characteristics that make patients more likely to be ineligible or unsuitable for chemotherapy.

Figure 6. Subgroup analysis for OS in TITAN (Final analysis; clinical cut-off date 7th September 2020; ITT population)

Abbreviations: CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; ITT: intent-to-treat; mHSPC: metastatic hormone-sensitive prostate cancer; NE: not estimable; OS: overall survival; PSA: prostate-specific antigen.
Source: TITAN FA TLR[10]

		There is no plausible biological reason why the effectiveness of apalutamide would be impacted by patient suitability for chemotherapy. The mechanism of action of apalutamide is clearly distinct to that of chemotherapy. Docetaxel expresses its antineoplastic activity by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly which leads to a marked decrease of free tubulin.(11) Apalutamide, by contrast, targets the androgen receptor, binds to it with high affinity and competitively inhibits androgen binding to the androgen receptor (AR) ligand-binding domain. It thereby blocks androgen-induced AR activation, prevents nuclear translocation, inhibits DNA binding and impedes AR-mediated transcription.(12) As such, apalutamide works well in all mHSPC patients, including those not suitable for docetaxel as it does not depend on a mode of action similar to that of docetaxel. Finally, the STAMPEDE trial provides evidence that is suggestive of an improved relative benefit of novel hormone therapy (abiraterone) in chemo-ineligible/unsuitable patients.(13) Within STAMPEDE, randomisations vary over time. For the early part of the abiraterone arm recruitment, the docetaxel arm was also recruiting, hence all patients recruited would have been fit for chemotherapy. However, from 2013, the docetaxel arm closed, so the requirement to be fit for chemotherapy no longer applied. Following 2013, recruitment rates to STAMPEDE increased and the average age of patients enrolled increased. It is reasonable to assume therefore that clinicians were now entering men who were not fit for chemotherapy. The respective hazard ratios for overall survival for these 2 groups were 0.69 and 0.59 respectively i.e. the hazard ratio for benefit improved when the “chemo-fitness” of the patients dropped.(13) Although not perfect evidence, these data are suggestive of at least a consistent treatment effect of novel hormone therapy in patients regardless of eligibility/suitability for chemotherapy.

		Summary Although perfect evidence for the effectiveness of apalutamide plus ADT in patients ineligible or unsuitable for docetaxel does not exist, it is reasonable to conclude that on the balance of probability, the relative effectiveness of apalutamide observed in TITAN is generalisable. This is because: 1. Chemo-ineligible/unsuitable patients represent the majority of mHSPC patients 2. Age and performance status are not treatment effect modifiers for apalutamide 3. Consistent effectiveness of novel hormone therapy has been demonstrated across a large number of clinical trials in mHSPC (TITAN, ARCHES, LATITUDE and STAMPEDE)
Key issue 3: extrapolation of survival curves: metastatic free survival (MFS) for nmHRPC and radiographic progression free survival (rPFS) for mHSPC	No	**3. Extrapolation of survival curves: metastatic free survival (MFS) for nmHRPC and radiographic progression free survival (rPFS) for mHSPC** Janssen acknowledges that uncertainty exists regarding the most appropriate extrapolations for MFS and rPFS. However, the SPARTAN and TITAN trials provide long-term follow-up data, with median MFS and rPFS outcomes reached for both the apalutamide + ADT and ADT alone arms of each trial at the time of the first data-cut for each study (given median MFS and rPFS were reached at the time of the first data-cut further data was not collected in subsequent data-cuts). Additionally, in accordance with the NICE DSU TSD 14 guidance on survival analyses[(14)] a wide range of factors were considered when selecting the most appropriate base-case survival curves to ensure that the most appropriate model was selected which included: • Inspection of log-cumulative hazard plot to determine which parametric models might be suitable (supported by Schoenfeld plots / the Schoenfeld test)

		• Visual inspection to assess the fit of the model to the Kaplan–Meier curve • Goodness-of-fit criteria including the Akaike information criterion (AIC) and the Bayesian information criterion (BIC) • Assessment of how the conditional survival probability changes over time • Assessment of how the assumed treatment effect changes over time • Clinical plausibility for both short- and long-term estimates of survival, based on clinical expert validation For MFS, all curves except for the Generalised-Gamma for ADT and exponential curve for apalutamide + ADT provided a good fit to the observed data. Given no other studies were identified which provided longer term MFS data that could help inform the extrapolations beyond the SPARTAN trial duration, clinical feedback on the survival curves was used to inform the longer-term extrapolations. Four clinical experts were consulted at an advisory board and came to the consensus that on balance the Weibull curves provided the most plausible long-term extrapolations. The clinicians noted that the Gompertz was too pessimistic for both treatments, whereas the log-logistic, log-normal and generalised gamma had implausibly long tails for ADT (and the exponential for apalutamide + ADT) as they predicted a proportion of patients would still be event free by years 20 and 30. For rPFS all curves appear to provide a good visual fit to the observed data. Although published survival data does exist for mHSPC which has been used to inform the OS extrapolations, there are issues with using this data to inform the progression free survival (PFS) extrapolations given the definitions of progression and the way these data were collected differs greatly between studies. Following a targeted literature search, only one trial was identified that reported rPFS data for patients with mHSPC, as the majority of studies reported data related to a different definition of progression or were in a different

		patient population. This study, Armstrong et al. 2019 reports data from the ARCHES trial which is less mature than TITAN and reports a median PFS of 19 months in the ADT alone arm, which is less than the median reported in TITAN (22.1 months). Given the absence of relevant external data the long-term extrapolations were informed based on clinical expert opinion. Feedback from five clinical experts was collected at an advisory board and the consensus was that although other curves may be plausible, the most appropriate on balance was the Weibull curve. The selection of the Weibull curve also has the advantage that it is consistent with the base-case curve selection for PFS2 and OS (which was informed by external data for mHSPC), and therefore consistent assumptions about the hazard function of each curve are made. It also ensures that the MFS/rPFS, PFS2 and OS curves do not cross at any time point. • The ERG note that the proportional hazards assumption is not supported by the trial data and, therefore, Weibull may not be the most suitable statistical distribution. However, as outlined in Issue 13 of the Proforma response document, an independently fitted Weibull model does not assume proportional hazards as both the shape and scale of the curve can vary. Instead, the Weibull assumes the hazard function can either increase or decrease monotonically. Additionally, the Weibull curve has consistently been selected as the Committee's preferred curve in previous submissions in prostate cancer, which include darolutamide in nmHRPC (TA660)[15] and abiraterone in newly diagnosed high risk mHSPC (ID945)[16], indicating that the assumed hazard function is reasonable.
Key issue 4: utility values for second and third-line metastatic hormone relapsed prostate cancer (mHRPC) health states	No	**4. Utility values for second and third-line metastatic hormone relapsed prostate cancer (mHRPC) health states** As the model is structured to distinguish between each line of treatment during the mHRPC phase, the model includes the functionality to use different utility values for each line of therapy. As patients move onto subsequent lines of therapy, it is assumed their health related quality of life (HRQL) declines over

		time in line with clinical expert opinion, and assumptions made in previous prostate cancer submissions. Given the number of EQ-5D questionnaires completed following disease progression from SPARTAN and TITAN were limited, it was necessary to use external data to inform the utility values for the 2L and 3L mHRPC health states. Therefore, in the base case analysis, estimates for second line and third line mHRPC were estimated using utility values from the TA387 submission. Given there will be differences in the patient population in TA387 and progressed patients from SPARTAN and TITAN, using the absolute utility values from TA387 as the ERG suggest would not have been appropriate. The estimates were therefore adjusted using the methods summarised in NICE DSU TSD 12, which outlines how to approach a situation when utility values from different data sources are used in the same analysis:[17] *"When health state utility values from cohorts with combined health conditions are not available, based on the current evidence, the multiplicative method should be used to combine the data derived from subgroups with the single health conditions."* This approach involved taking the 2L and 3L mHRPC utility values reported in TA387[18] (0.625 and 0.5 respectively) and dividing them by the 1L mHRPC utility value ([redacted]) to estimate the decline in HRQL of moving from the 1L to 2L, and the 2L to 3L health states. These ratios were then multiplied by the progressed utility values from SPARTAN and TITAN to calculate 2L and 3L utility values that were applied in the model. This is the same approach that was accepted by the appraisal committee in NICE ID945.(16) The aim of this approach is to adjust the utility values for 2L and 3L mHRPC for differences between the populations in each study.

The ERG's proposed approach of using the utility values with no adjustment can produce results that lack face validity as it does not adjust for the differences between the populations in the different studies. For example, the scenario presented by the ERG which applies utility values from TA580[19] assumes that HRQL improves as patients progress from 1L to 2L mHRPC which lacks clinical validity. A summary of the different utility values applied in each scenario is presented in Table 13.

Table 13: Summary of the utility values applied by the company and ERG

	Company estimates		ERG estimates: TA387		ERG estimates: TA377		ERG estimates: TA580	
	nmHRPC	mHSPC	nmHRPC	mHSPC	nmHRPC	mHSPC	nmHRPC	mHSPC
Pre-progression	[redacted]	[redacted]	0.8233	0.805	0.8233	0.805	0.8233	0.805
mHRPC Treatment L1	[redacted]	[redacted]	0.771	0.698	0.771	0.698	0.771	0.698
mHRPC Treatment L2	[redacted]	[redacted]	0.625	0.625	0.612	0.612	0.800	0.800
mHRPC Treatment L3	[redacted]	[redacted]	0.500	0.500	0.500	0.500	0.688	0.688

Abbreviations: L1, first-line; 2L second-line; L3, third-line; mHSPC, metastatic hormone-sensitive prostate cancer; nmHRPC, non-metastatic hormone-relapsed prostate cancer

The estimates from TA387 were selected after reviewing the data available from different NICE submissions in prostate cancer. A summary of the review that was conducted is presented in Table 31 of the company response to ERG clarification questions document, with the ERG presenting their own findings in Table 36 of the ERG report (presented in Table 14).

A number of the submissions did not report complete information as some of the utility values had been redacted. The only submissions which reported a full set of utility values for the 1L, 2L and 3L mHRPC health states were ID945[16], which adopted the exact same approach of using adjusted estimates from

		TA387 (and TA377[20] which reported utility values which were almost identical to the estimates from TA387). Although the full set of values were not reported for TA580[19], the ERG identified that utility values were reported in SMC documentation, but it is not clear if these estimates are consistent with the Committee's preferred estimates that were presented as part of the NICE submission. Additionally, using these estimates assumes that there is no meaningful decrease in utility as patients progress from 1L to 2L mHRPC, which is not consistent with the assumptions made in other appraisals.

Table 14: Health state utility values for mHRPC from previous NICE appraisals (Table 36 of the ERG report)

Appraisal	Utility values
ID945: Abiraterone	High risk mHSPC: 0.792 1L mHRPC: 0.704 2L mHRPC: 0.525 3L mHRPC: 0.420 Note the mHRPC utility values were calculated using the exact same method that is outlined in the response to clarification question B15
TA580: Enzalutamide	1L mHRPC: 0.81[a] 2L mHRPC: 0.8 [a] 3L mHRPC: 0.688 End-of-life utility: 0.590 (applied for 3 months period prior to death)
TA391: Cabazitaxel	mHRPC (stable disease): 0.704-0.819 mHRPC (progressive disease): 0.6266 (until last 3 months of life which are set to 0)
TA387: Abiraterone	1L mHRPC: 0.83 2L mHRPC: 0.625 3L mHRPC: 0.5
TA377: Enzalutamide	mHRPC (stable disease): 0.844 Post progression 1: 0.658 Post progression 2: 0.612 Palliative care: 0.5
TA316: Enzalutamide	mHRPC (Disutility progression): -0.085
TA259: Abiraterone	Pre-progression: 0.780 mHRPC (Post-progression): 0.5

Key: 1L, first line, 2L, second-line, 3L, third-line, mHRPC, metastatic hormone relapsed prostate cancer.
[a] Values reported in the Scottish Medicines Consortium appraisal of enzalutamide for nmHRPC

Key issue 5: market share of subsequent therapies used in metastatic hormone relapsed prostate cancer (mHRPC)	No	**5. Rationale for advisory board used** The selection of subsequent treatments and their sequencing reflects clinical practice in the UK and was based on NICE guidance and expert clinical opinion.[21-23] 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 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. • The market shares used in the base case were sourced from the mHSPC advisory board. The values from the advisory board were applied in the base-case instead of the trial data as this is most reflective of the treatments given to patients in UK clinical practice and accounts for the one novel therapy commissioning policy. The values from the mHSPC advisory board were preferred to the nmHRPC advisory board estimates as they provided more up to date estimates given the timing of the advisory boards (June 2019 vs December 2018), because the advisory board consulted a larger number of clinicians (five vs four), and because use of these market share estimates also provided results which were more conservative. These estimates are also broadly consistent with the market shares presented as part of the darolutamide submission in nmHRPC (TA660).[15] **Subsequent treatment with docetaxel** Clinicians at the advisory board for mHSPC noted that a percentage of patients who are unsuitable for or unwilling to receive chemotherapy could receive docetaxel following disease progression. This is partly because patients who were previously considered to be unfit for chemotherapy may respond well to the treatment they received in mHSPC, and therefore could be considered suitable for treatment in the

		mHRPC setting. This point is also highlighted by the clinical community in the recent appeal decision document for abiraterone in newly diagnosed high risk mHSPC (ID945)[24]: *"For example, some people might not receive chemotherapy early in their disease but would receive it later if their fitness changed." page 14, paragraph 92*
Key issue 6: Duration of adverse event costs for docetaxel (mHSPC)	Yes	**6. Duration of adverse event costs for docetaxel (mHSPC)** Costs associated with managing Grade 3–4 adverse events that occurred during the treatment phase and were classed as all-cause/treatment-related were included in the cost-effectiveness analysis. The frequency of each adverse event was calculated from the adverse event incidence in the clinical trials. A rate for each event per model cycle was estimated by dividing the total incidence from each study by the total median trial follow-up in weeks so that the costs could be applied over the time horizon of the model. The per cycle adverse event rate for patients in the pre-progression health state who received docetaxel + ADT was calculated from the Gravis et al. 2013[25] study which presents adverse event rates reported in the first six months of treatment. We accept that applying these rates throughout the entire pre-progression health state may lead to an overestimate of the costs of managing adverse events. However, the ERG's approach of only applying adverse event costs for the first six months results in an underestimate of these costs for several reasons. Firstly, the ERG only applied costs in the first six months to those in the pre-progression health state, which assumes that patients after six months do not experience any adverse events. This is clinically implausible given these patients will continue to be treated with ADT which is associated with adverse events. It is also conservative to assume that the costs incurred through treating these adverse events

		will fall to zero at six months as the impact of many grade 3-4 events on a patient will likely continue long after the event was first experienced. This approach also doesn't account for the fact that adverse event rates were only collected for six months due to the design of the study, which does not mean that patients did not experience any adverse events from this point onwards. Secondly, the adverse event rates reported in Gravis et al. 2013[25] for docetaxel applied in the model are potentially underestimated. Real-world data on the usage of docetaxel plus ADT, since it became routinely available through the NHS, report that the rates of Grade ≥ 3 neutropenia and febrile neutropenia were 36.3% and 18.2% respectively (compared to 32% and 7% reported in Gravis et al. 2013).[26] Further real world evidence supports this, with a UK single-centre report of the outcomes of 39 patients stated that that 36% of patients (14 out of 39) treated with docetaxel experienced grade 3 or 4 neutropenia and 20% of patients (8 out of 39 patients) experienced neutropenic sepsis.[27] Similarly, in a different UK single-centre report, 30% of patients (16 out of 53) experienced febrile neutropenia.[28] These findings suggest that the side effects associated with docetaxel treatment in patients with mHSPC may be more frequent in routine clinical practice than is reported in clinical trials. Furthermore, during the COVID-19 pandemic, the EU released guidance to avoid the use of docetaxel as it is a chemotherapy that could compromise the immune system.(29) This guidance, although not formally accounted for in the economic analysis, further supports the argument that the side effects suffered by patients due to use of docetaxel are of real consequence.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Updated clinical effectiveness results from TITAN, NMA and cost effectiveness analyses (using ERG preferred assumptions where appropriate)	N/A	Yes	These updates are presented in Section 7-9 below.

7. TITAN Final analysis update.

These data are based on a clinical cut-off date of 7th September 2020

With a median follow-up of [redacted] months ([redacted] months more than at the time of the interim analysis), [redacted] deaths had occurred. After unblinding, [redacted] of patients in the placebo group have crossed over to receive open-label apalutamide. The median survival was [redacted] months for placebo group; the median was not reached for apalutamide group. Updated analysis of survival confirmed the benefit observed at the time of interim analysis, (HR=[redacted] [95% CI [redacted]).

The final analysis of rPFS was planned after 368 events which was reached after the interim analysis. rPFS and HRQL endpoints have been presented previously and as such are not repeated within this update.

Patient disposition and treatment exposure

A total of 525 patients were randomly assigned to receive apalutamide plus ADT and 527 to receive placebo plus ADT. In January 2019, the Independent Drug Monitoring Committee (IDMC) recommended unblinding of the trial. Following unblinding, [redacted] patients in the placebo plus ADT arm were offered the opportunity to receive apalutamide. [redacted] ([redacted] of the placebo plus ADT arm) have crossed over to receive open-label apalutamide. At final analysis data cut, [redacted] patients originally randomised to receive apalutamide plus ADT and [redacted] of crossover patients continued treatment with apalutamide. As such, this could have introduced some degree of bias against apalutamide plus ADT at final analysis.

Progressive disease was the most common reason for treatment discontinuation. Median treatment duration was [redacted] and [redacted] months for apalutamide, placebo and crossover groups, respectively.

Overall survival

At the time of final analysis, [redacted] deaths were observed: [redacted] in the apalutamide plus ADT group and [redacted] in the placebo plus ADT group. As shown in Table 15 and Figure 7, median OS was not reached in the apalutamide plus ADT group (95% CI: (not estimable [NE]-NE) and was [redacted] months (95% CI: [redacted]) in the placebo plus ADT group. Treatment with apalutamide plus ADT resulted in a [redacted] reduction in the risk of death compared with placebo plus ADT (HR=[redacted] [95%CI: [redacted]), despite permitted crossover after the trial was unblinded. At the time of final analysis, the majority ([redacted]) of patients in the apalutamide plus ADT group were still alive, compared to [redacted] of patients in the placebo plus ADT group, reaffirming the sustained survival benefit of apalutamide plus ADT.

Table 15. Summary of OS in the TITAN trial (Final analysis; clinical cut-off date 7th September 2020; ITT population)

	Placebo plus ADT (n=527)	**Apalutamide plus ADT (n=525)**
Events (%)	[redacted]	[redacted]
Censored	[redacted]	[redacted]
Time to event (months)		
25th percentile (95% CI)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
75th percentile (95% CI	[redacted]	[redacted]
	[redacted]	[redacted]
6-month event-free rate, % (95% CI)	[redacted]	[redacted]
12-month event-free rate, % (95% CI)	[redacted]	[redacted]
24-month event-free rate, % (95% CI)	[redacted]	[redacted]
36-month event-free rate, % (95% CI)	[redacted]	[redacted]
48-month event-free rate, % (95% CI)	[redacted]	[redacted]
HR (95% CI)[b]	[redacted]	
p value[c]	[redacted]	

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; HR, hazard ratio; ITT, intent to treat; NE, not estimable; OS, overall survival
Notes: [a] censored observation
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favours active treatment.
[c] p-value is from the log-rank test stratified by Gleason score at diagnosis (≤7 vs. >7), Region (NA/EU vs. Other Countries) and Prior docetaxel use (Yes vs. No).
Source: TITAN FA TLR 2020[(10)]

Figure 7. Kaplan-Meier plot of OS in the TITAN trial (Final analysis; clinical cut-off date 7th September 2020; ITT population)

Abbreviations: FA, final analysis; ITT, intention to treat; OS, overall survival
Source: TITAN FA TLR 2020[10]

Subgroup analysis

The point estimates of the treatment effect of apalutamide on OS were favourable (HR<1) for all subgroups except prior docetaxel use and consistent with the overall study results.

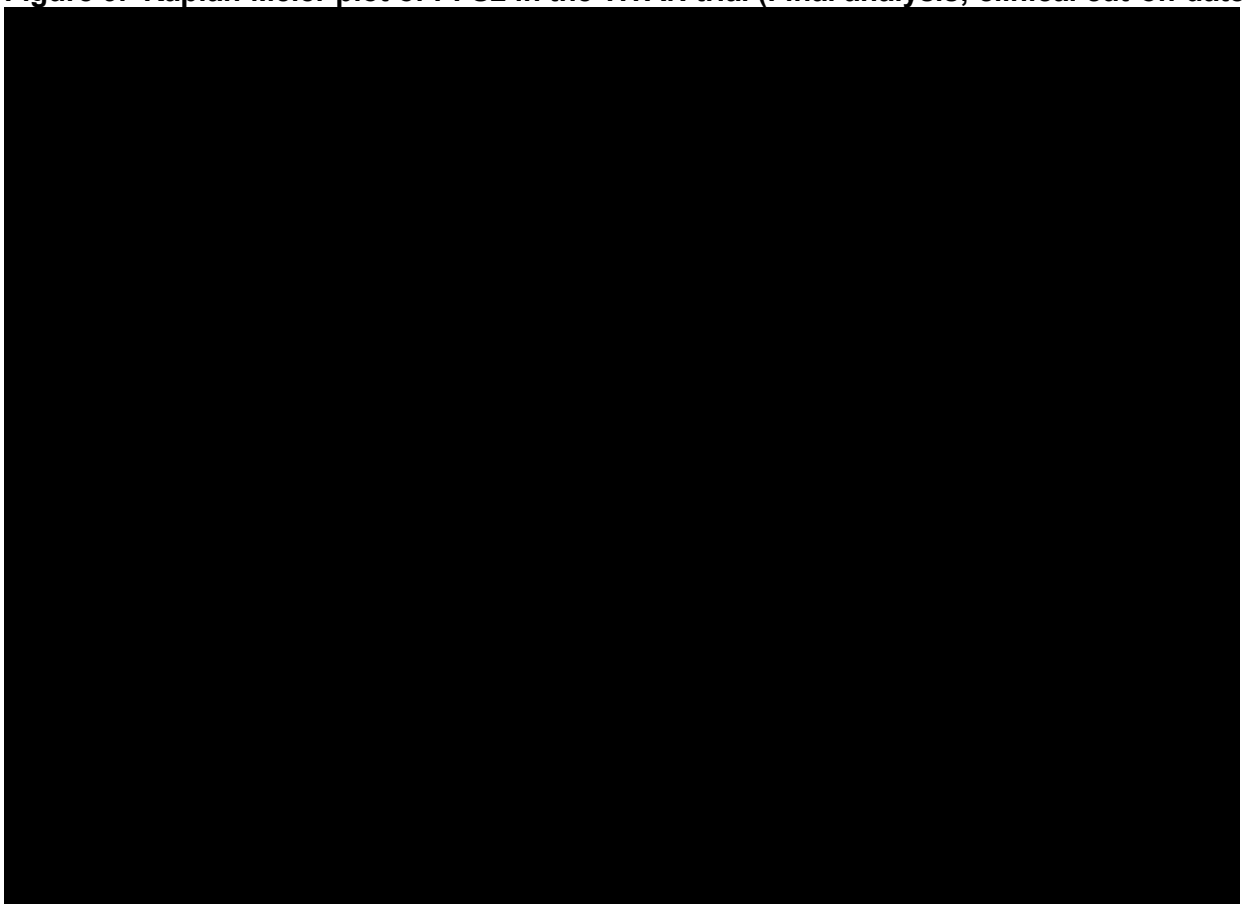
Figure 8. OS subgroup analysis in the TITAN trial (Final analysis; clinical cut-off date 7th September 2020; ITT population)

Abbreviations: CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; EU: European Union; ITT: intent-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[10]

PFS2 (exploratory endpoint)

At final analysis, treatment with apalutamide plus ADT was associated with a 34% reduction in the risk of PFS2 compared with placebo plus ADT (HR= [redacted], 95% CI ([redacted]), [redacted]) as shown in Figure 9. This result is consistent with the benefit observed at the interim analysis (HR = 0.66; 95% CI: 0.50, 0.87; p < 0.0026).

Figure 9. Kaplan-Meier plot of PFS2 in the TITAN trial (Final analysis; clinical cut-off date 7th September 2020; ITT population)



Abbreviations: APA, apalutamide; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NE, not-estimable; PFS2, second progression-free survival
Notes. aBased on unstratified analysis. bBased on stratified analysis (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)

Subsequent therapies

At final analysis, [redacted] of patients in apalutamide plus ADT arm and [redacted] of patients in placebo and ADT arm had received subsequent therapy after discontinuation from study treatment. Subsequent therapies that are considered life-prolonging are presented in Table 16 with docetaxel and abiraterone plus prednisone the most frequently administered as subsequent therapy.

Table 16**. Selected subsequent therapy for prostate cancer in the TITAN trial (Final analysis; clinical cut-off date 7th September 2020; ITT population)**

	Placebo plus ADT (n=527)	Apalutamide plus ADT (n=525)
Number of subjects alive at treatment discontinuation (denominator for table below)	[redacted]	[redacted]
Number of subjects with selected subsequent therapy for prostate cancer	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]
Abiraterone	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]
Cabazitaxel	[redacted]	[redacted]
Radium 223	[redacted]	[redacted]
Sipuleucel-T	[redacted]	[redacted]
Cabazitaxel Acetone	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; ITT, intention-to-treat

Secondary endpoints

The updated analyses were performed for the secondary and other efficacy endpoints based on the updated data. The results are presented in Table 17. Updates on secondary endpoints are for descriptive purposes; hierarchical testing or any inferential statistics for any of the secondary endpoints is not applicable.

Table 17. Summary of the results of secondary endpoints in the TITAN trial (Final analysis; clinical cut-off date 7th September 2020; ITT population)

	Placebo plus ADT		Apalutamide plus ADT		HR (95% CI)	*P* value
	Event (%)	Median (months)	Event (%)	Median (months)		
Time to Initiation of Cytotoxic Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to Pain Progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to Chronic Opioid Use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to SRE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; NE, not estimable; SRE, skeletal related events

Notes: Updated analyses for the secondary endpoints for descriptive purposes with updated data on these endpoints; hierarchical testing or any inferential statistics for any of the secondary endpoints is not applicable

Updated safety analysis

The results from the final analysis were consistent with those presented in the interim analysis. A summary of the treatment emergent adverse events is presented in Table 18 . The number of subjects with treatment-emergent adverse events with frequency of at least 10% in any treatment group are presented in Table 19.

Table 18. Overall Summary of Treatment-emergent Adverse Events in the TITAN trial (Final analysis; clinical cut-off date 7th September 2020; safety population)

	Placebo plus ADT (n = 527)	Apalutamide plus ADT (n = 524)
TEAEs, total, n (%)	[redacted]	[redacted]
TEAEs, drug-related, n (%)	[redacted]	[redacted]
TEAEs, Grade 3-4, n (%)	[redacted]	[redacted]
TEAEs, Grade 3-4, drug-related, n (%)	[redacted]	[redacted]
SAEs, total, n (%)	[redacted]	[redacted]
SAEs, drug-related, n (%)	[redacted]	[redacted]
SAEs, Grade 3-4, n (%)	[redacted]	[redacted]
TEAE-related discontinuation, n (%)	[redacted]	[redacted]
TEAE-related discontinuation, drug-related, n (%)	[redacted]	[redacted]
TEAE-related deaths, n (%)	[redacted]	[redacted]
TEAE-related deaths, drug-related, n (%)	[redacted]	[redacted]
Deaths within 30 days of last dose, n (%)	[redacted]	[redacted]
Death due to prostate cancer, n (%)	[redacted]	[redacted]
Death due to AE, n (%)	[redacted]	[redacted]

Abbreviations: ADT: androgen deprivation therapy; AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event
Notes: AEs and concomitant therapies were assessed continually from informed consent until 30 days after the last dose of study drug.

Table 19. Number of Subjects with Treatment-emergent Adverse Events With Frequency of at Least 10% in any Treatment Group by System Organ Class and Preferred Term in the TITAN trial (Final analysis; clinical cut-off date 7th September 2020; safety population)

Analysis set: Safety population	Placebo plus ADT (n = 527)	Apalutamide plus ADT (n = 524)
Patients with 1 or more TEAEs	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Bone pain	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Hot flush	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]

Anaemia	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; TEAEs, treatment emergent adverse events
Notes: Table does not include grade 5 event

8. NMA update

The network meta-analyses (NMA) presented in the original submission were updated following the availability of the TITAN final analysis data. Of the outcomes originally included, rPFS and time to prostate-specific antigen (PSA) progression were not updated in the latest data cut for TITAN and as such only OS and safety (adverse events [AEs] and serious adverse events [SAEs]) were included in this NMA update. The sources of data for the three outcomes in this NMA update are summarised in Table 20.

Table 20. Sources of data for the NMA update

Trial	OS		AEs		SAEs	
	Time point (months)	Publication	Time point (months)	publication	Time point (months)	publication
TITAN	[redacted]	TITAN FA 2020	[redacted]	TITAN FA 2020	[redacted]	TITAN FA 2020
CHAARTED	28.9	Sweeney 2015				
GETUG-AFU 15	50	Gravis 2013				
STAMPEDE (Arms C vs. A)	43	James 2016	78.2	STAMPEDE IPD	78.2	STAMPEDE IPD

Abbreviations: AE, adverse events; IPD, individual patient data; NMA, network meta-analysis; OS, overall survival; SAEs, serious adverse events
Sources: Gravis 2013,[25] Gravis 2016,[30] James 2016,[31] Sweeney 2015,[32], TITAN FA TLR[10]

Aggregate outcome measures, HRs and 95% CIs for OS and odds ratios (ORs) and 95% CIs from each trial were synthesised in the NMA. Where STAMPEDE individual patient level data (IPD) was included (for AEs and SAEs), the IPD was first aggregated into study level data prior to inclusion in the NMA in the same way as aggregate data from published sources.

Both a fixed-effect (FE) and random-effect (RE) models were developed. Due to the limited number of studies available to inform each treatment comparison, the FE model is considered more appropriate and as such was used for the base case analysis. Results from a RE model with a prior distribution (U[0,1]) are presented as a sensitivity analysis. To be consistent with the additional analyses presented at clarification questions stage following a request from the ERG, results from a RE model using a more informative prior (U[0.0.4]) are also presented to assess the sensitivity of the model to the choice of prior distribution.

Updated subsequent therapies in NMA trials

Table 39 in document B of the original submission summarising subsequent therapies received in the four trials was updated to include subsequent therapy information from the final analysis datacut for TITAN and is shown in Table 21. More patients in both treatment arms had received subsequent therapies in TITAN at final analysis than at the interim analysis. A greater proportion of these were in the placebo plus ADT arm however, and this, together with the substantial level of crossover from the placebo plus ADT arm to the apalutamide plus ADT arm observed in the trial mean that any potential bias in the NMA results is such that the treatment effect of apalutamide plus ADT versus ADT and versus docetaxel plus ADT is underestimated

Table 21: Summary of subsequent therapies received in the respective trials updated with TITAN FA

Treatment	CHAARTED [a]		GETUG-AFU 15 [b]		STAMPEDE [c]		TITAN Interim Analysis[d]		TITAN Final Analysis[d]	
	ADT alone (n=287)	Docetaxel plus ADT (n=238)	ADT alone (n=149)	Docetaxel plus ADT*	ADT alone (n=535)	Docetaxel plus ADT (n=238)	Placebo plus ADT (n=190)	Apalutamide plus ADT (n=87)	Placebo plus ADT (n=221)	Apalutamide plus ADT (n=120)

Proportion receiving subsequent therapies[e]	73.%	60%	77%	0.00	74%	66%	36%	17%	[redacted]	[redacted]
Abiraterone acetate			36 (24%)	33	177 (23%)	89 (28%)	45 (24%)	21 (24%)	[redacted]	[redacted]
Cabazitaxel	37 (13%)	57 (24%)	15 (10%)	16	26 (3%)	22(7%)	2 (1%)	1 (1%)	[redacted]	[redacted]
Docetaxel	137 (48%)	54 (23%)	127 (85%)		313 (41%)	44 (14%)	67 (35%)	29 (33%)	[redacted]	[redacted]
Enzalutamide			12 (8%)	15	66 (9%)	25 (8%)	17 (9%)	3 (3%)	[redacted]	[redacted]
Radium-223					6(1%)	6 (2%)	4 (2%)	2 (2%)	[redacted]	[redacted]
Sipuleucel-T							4 (2%)	2 (2%)	[redacted]	[redacted]
Abiraterone and/or enzalutamide	104 (36%)	105 (44%)								

Abbreviations: ADT, androgen deprivation therapy
Notes: [a] Source, Sweeney 2015(4), percentages are calculated from those with serological progression/clinical progression. Numbers for clinical progression only are ADT 228 and ADT+D 180.
[b] Source, Gravis 2016 (2), * the paper reports 27/149 treated for progressive disease in the ADT arm. Unclear how many patients were treated for progression in the ADT+D arm therefore % for this could not be reported
[C] Source, James 2017(6), percentages calculated from the numbers with progression
[d] Source Chi 2019(7), percentages are calculated from patients receiving subsequent systemic therapy following radiographic progression.
[e] Calculated from patients randomised into each treatment arm

Updated results

A comparison of the base case OS and safety NMA results across the two TITAN data cuts is shown in Table 22. Consistent with the evidence from TITAN, the OS HR for apalutamide plus ADT versus ADT has improved in favour of apalutamide from the interim to the final analysis. The same is true for apalutamide plus ADT versus docetaxel plus ADT with the OS HR improving from [redacted], 95% credible interval (CrI) [[redacted]; [redacted]] based on data from the interim analysis to [redacted], 95% CrI [[redacted]; [redacted]] based on data from the final analysis data cut.

Detailed updated results are presented in the following sections

Table 22. Comparison of base case OS and safety NMA results across the interim and final analysis data cuts of TITAN

Comparison	Interim Analysis			Final Analysis update		
	OS	AE	SAEs	OS	AE	SAEs
Apalutamide + ADT vs ADT HR [95% CrI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apalutamide + ADT vs Docetaxel + ADT HR [95% CrI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; AE, adverse events; CrI, credible interval; HR, hazard ratio; OS, overall survival; SAEs, serious adverse events

Updated OS NMA results

The OS results from the FE and RE models are displayed in Table 23. The results from the FE NMA suggest that apalutamide plus ADT offers an advantage over ADT alone, with median HR (95% CrI) of [redacted] and is favourable versus docetaxel plus ADT [redacted]. There was a [redacted]% Bayesian probability of apalutamide plus ADT being a better treatment than ADT alone and an [redacted]% probability of apalutamide plus ADT being the better treatment versus docetaxel plus ADT.

The results from the RE models support those generated in the base case using the FE model, with point estimates identical for both approaches. Compared to the FE models, a wider variation in the 95% CrIs was observed in the RE models as would be expected.

Table 24 displays the surface cumulative ranking curve (SUCRA) values for OS. In all models (FE and RE) apalutamide was associated with the highest values.

Table 23: NMA OS results based on fixed and random effects models

Comparison		FE	RE models (u[0,1])	RE models (u[0,0.4])
Apalutamide plus ADT vs ADT alone	HR (95% CrI)	[redacted]	[redacted]	[redacted]
	Probability that HR is less than 1	[redacted]	[redacted]	[redacted]
Apalutamide plus ADT vs docetaxel plus ADT	HR (95% CrI)	[redacted]	[redacted]	[redacted]
	Probability that HR is less than 1	[redacted]	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; CrI, credible interval; FE, fixed effects; HR, hazard ratio; NMA, network meta-analyses; OS, overall survival; RE, random effects

Table 24: NMA OS SUCRA for fixed and random effects models

Comparator	SUCRA for FE models	SUCRA for RE models (u[0,1])	SUCRA for RE models (u[0,0.4])
Apalutamide plus ADT	[redacted]	[redacted]	[redacted]
Docetaxel plus ADT	[redacted]	[redacted]	[redacted]
Placebo plus ADT	[redacted]	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; FE, fixed effects; NMA, network meta-analyses; OS, overall survival; RE, random effects; SUCRA, surface under the cumulative ranking curve;

Sensitivity analysis on OS NMA using the latest data cut for each trial

As in the original submission, a sensitivity analysis was conducted to assess the impact on the results of using the latest available data for each trial and the final analysis data-cut for TITAN. Results of the sensitivity analysis on OS show that the HR for apalutamide plus ADT is consistent with that in the base case and the HR point estimates for apalutamide plus ADT versus docetaxel plus ADT are lower than those in the base case for the FE and RE models (Table 25). The SUCRA values for all the OS NMA models consistently show that apalutamide plus ADT is most likely to be the best treatment (Table 26).

Table 25. NMA OS results: fixed and random effects models using the latest available data-cut for each trial (sensitivity analysis)

Comparison		FE	RE models (u[0,1])	RE models (u[0,0.4])
Apalutamide plus ADT vs ADT alone	HR (95% CrI)	[redacted]	[redacted]	[redacted]
	Probability that HR is less than 1	[redacted]	[redacted]	[redacted]
Apalutamide plus ADT vs docetaxel plus ADT	HR (95% CrI)	[redacted]	[redacted]	[redacted]
	Probability that HR is less than 1	[redacted]	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; CrI, credible interval; FE, fixed effects; HR, hazard ratio; NMA, network meta-analyses; OS, overall survival; RE, random effects

Table 26: NMA OS SUCRA for fixed and random effects models using the latest available data-cut for each trial (sensitivity analysis)

Comparator	SUCRA for FE models	SUCRA for RE models (u[0,1])	SUCRA for RE models (u[0,0.4])
Apalutamide plus ADT	[redacted]	[redacted]	[redacted]

Docetaxel plus ADT	[redacted]	[redacted]	[redacted]
Placebo plus ADT	[redacted]	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; FE, fixed effects; NMA, network meta-analyses; OS, overall survival; RE, random effects; SUCRA, surface under the cumulative ranking curve

Updated Safety NMA results

As presented in Table 27, apalutamide plus ADT demonstrated favourable results versus docetaxel plus ADT with a [redacted]% probability of lower odds of experiencing any AEs. In terms of SAEs apalutamide plus ADT demonstrated superiority over docetaxel plus ADT, with a [redacted]% probability that the OR is less than 1. The odds of a serious adverse event are [redacted]% lower with apalutamide plus ADT compared to docetaxel based upon this NMA. Given the strong patient preference for treatments that extend length of life without impacting quality of life, this result highlights the suitability of apalutamide as a treatment option in all mHSPC patients. Moreover, a substantial percentage of mHSPC patients currently do not receive docetaxel as they are considered ineligible or otherwise unsuitable. The risk of SAEs is a key driver in the shared decision between a patient and their clinician regarding docetaxel as a treatment option. The benefit of apalutamide with respect to the reduced risk of SAEs versus docetaxel plus ADT, along with the benefit of apalutamide pertaining to efficacy over ADT means apalutamide is a highly beneficial treatment option for patients ineligible, or otherwise unsuitable, for docetaxel.

SUCRA values support these conclusions (Table 28). Apalutamide plus ADT had higher values for both overall AEs and SAEs than docetaxel plus ADT.

Table 27: NMA safety outcomes fixed effects model

Comparison		**Overall AEs**	**SAE**
Apalutamide plus ADT vs ADT alone	Median OR (95% CrI)	[redacted]	[redacted]
	Probability that OR is less than 1	[redacted]	[redacted]

Apalutamide plus ADT vs Docetaxel plus ADT	OR (95% CrI)	[redacted]	[redacted]
	Probability that OR is less than 1	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; AE, adverse events; CrI, credible intervals; NMA, network meta-analyses; SAE, serious adverse events.

Table 28: NMA SUCRA for safety fixed effects model

Comparator	SUCRA for overall AEs	SUCRA for SAE
Placebo plus ADT	[redacted]	[redacted]
Apalutamide plus ADT	[redacted]	[redacted]
Docetaxel plus ADT	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; AE, adverse events; NMA, network meta-analyses; SAE, serious adverse events; SUCRA, surface under the cumulative ranking curve

For sensitivity analysis, safety results and SUCRA from the RE model U[0,1] are presented in Table 29 and Table 30 and results and SUCRA from the RE model U[0, 0.4] are presented in Table 31 and Table 32.

OR point estimates from the RE models were consistent with those from the FE model for both safety endpoints whilst as expected, credible intervals were wider than those observed in the FE model.

Table 29: NMA safety results, RE model, U[0,1]

Comparison		Overall AEs	SAE
Apalutamide plus ADT vs ADT alone	Median OR (95% CrI)	[redacted]	[redacted]
	Probability that OR is less than 1	[redacted]	[redacted]

Apalutamide plus ADT vs Docetaxel plus ADT	OR (95% CrI)	[redacted]	[redacted]
	Probability that OR is less than 1	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; AE, adverse events; CrI, credible intervals; NMA, network meta-analyses; RE, random effects; SAE, serious adverse events.

Table 30: NMA SUCRA for safety, RE model, U[0,1]

Comparator	SUCRA for overall AEs	SUCRA for SAE
Placebo plus ADT	[redacted]	[redacted]
Apalutamide plus ADT	[redacted]	[redacted]
Docetaxel plus ADT	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; AE, adverse events; NMA, network meta-analyses; RE, random effects; SAE, serious adverse events; SUCRA, surface under the cumulative ranking curve

Table 31: NMA safety results, RE model (u[0,0.4])

Comparison		Overall AEs	SAE
Apalutamide plus ADT vs ADT alone	Median OR (95% CrI)	[redacted]	[redacted]
	Probability that OR is less than 1	[redacted]	[redacted]
Apalutamide plus ADT vs Docetaxel plus ADT	OR (95% CrI)	[redacted]	[redacted]
	Probability that OR is less than 1	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; AE, adverse events; CrI, credible intervals; NMA, network meta-analyses; RE, random effects; SAE, serious adverse events.

Table 32: NMA SUCRA for safety, RE model (u[0,0.4])

Comparator	SUCRA for overall AEs	SUCRA for SAE
Placebo plus ADT	[redacted]	[redacted]
Apalutamide plus ADT	[redacted]	[redacted]
Docetaxel plus ADT	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; AE, adverse events; NMA, network meta-analyses; RE, random effects; SAE, serious adverse events; SUCRA, surface under the cumulative ranking curve

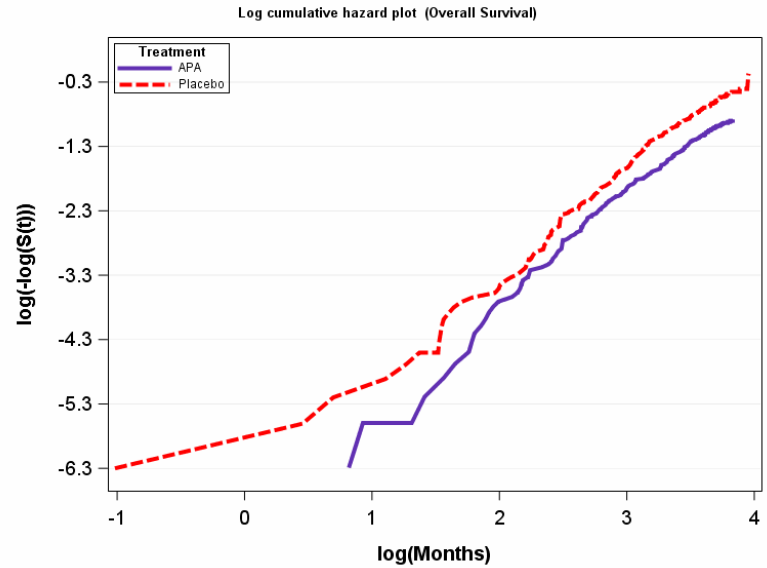
Proportional hazards test

An assessment for proportional hazards (PH) for OS was previously conducted for the docetaxel trials as well as for the TITAN interim analysis.

Please refer to Appendix D to the original company submission for the results.

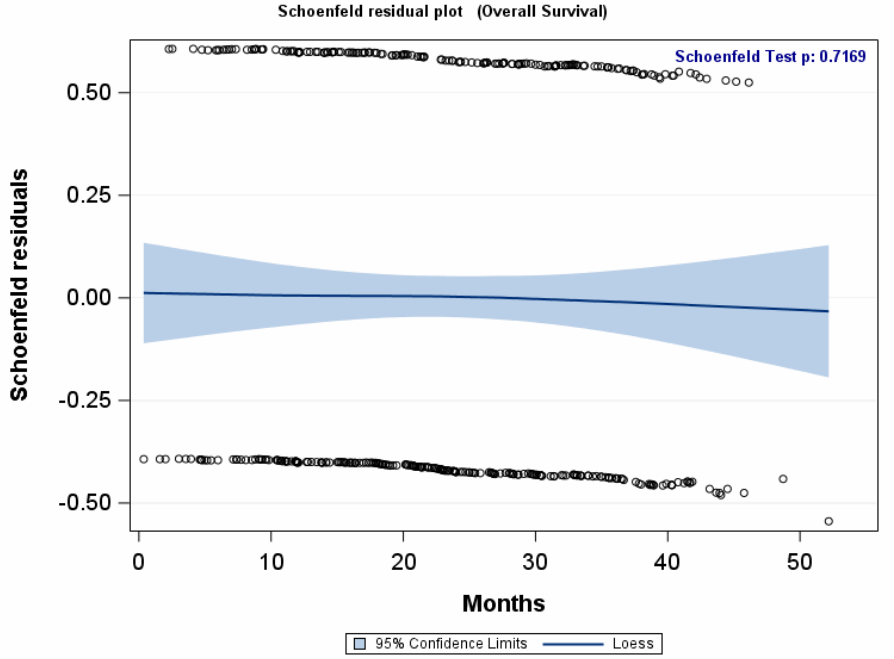
A follow-up assessment was conducted on TITAN final analysis OS data to test if the assumption for PH still held. This was found to be the case as illustrated by the parallel curves in the log cumulative plot in Figure 10 as well as the Schoenfeld residuals p value of p=0.7169 as shown in Figure 11.

Figure 10. Log cumulative hazard plot for OS in TITAN (Final analysis, clinical cut-off date 7 September 2020, ITT population)



Abbreviations: APA, apalutamide; ITT, intention to treat population; OS, overall survival

Figure 11. Schoenfeld residual plot for OS in TITAN (Final Analysis, clinical cut-off date 7 September 2020, ITT population)



Abbreviations: ITT, intention to treat population; OS, overall survival

9. Updated cost-effectiveness results

9.1. Projection of survival beyond the clinical trials

Additional extrapolations of the PFS2 and OS data from SPARTAN and TITAN have been estimated following the original submission. For nmHRPC, additional methods have been used to adjust the survival data simultaneously for treatment crossover as well as for the one novel therapy restriction as outlined in Section 1. For mHSPC, data from the TITAN final analysis presented in Section 7 has been used to update the

extrapolations that were presented in the original submission, and to produce new extrapolations using the additional treatment crossover methods.

nmHRPC

Figure 12 to Figure 14 present the PFS2 and OS KM data that has been adjusted using the different methods outlined in Section 1. The results of the IPCW analysis are considered inappropriate as it results in a significant increase in the treatment effect for apalutamide plus ADT following adjustment. For OS there is consistency between the KM curves that have been adjusted using the COU-AA-302 data from the FA data-cut and IA3. Therefore, the base-case approach remains unchanged from the original submission (RPFSTM using COU-AA-302 FA). The extrapolated curves for the alternative RPSFTM scenario for SPARTAN are presented in Appendix A alongside the extrapolated curves for TITAN FA.

Figure 12. Kaplan-Meier plot of PFS2 (with additional crossover adjustment methods; SPARTAN final analysis)

Abbreviations: ADT: androgen deprivation therapy; APA: apalutamide; IPCW: inverse probability of censoring weights; RPSFTM: rank preserving structural failure time model.

Figure 13. Kaplan-Meier plot of OS (with additional crossover adjustment methods; SPARTAN final analysis): APA + ADT

Abbreviations: ADT: androgen deprivation therapy; APA: apalutamide; IPCW: inverse probability of censoring weights; RPSFTM: rank preserving structural failure time model.

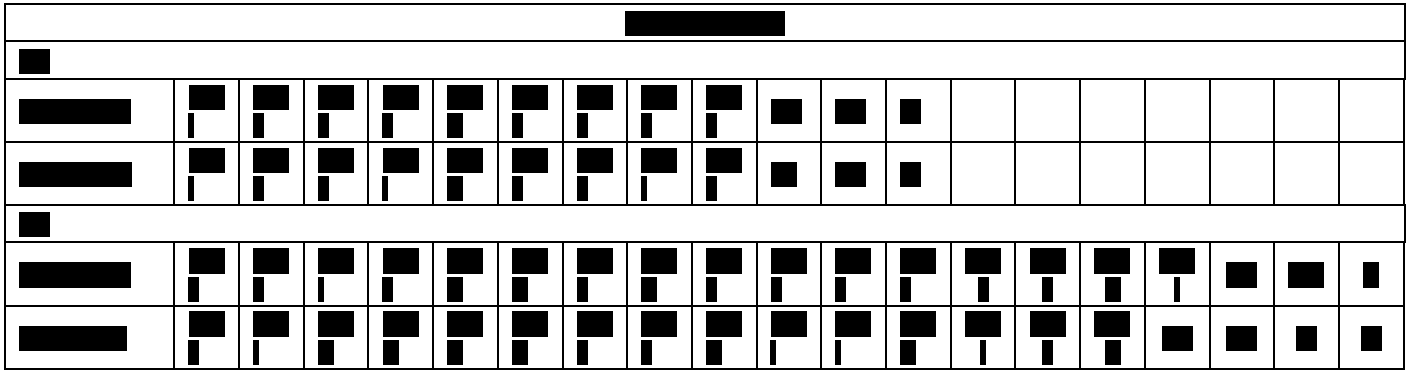
Figure 14. Kaplan-Meier plot of OS (with additional crossover adjustment methods; SPARTAN final analysis): ADT alone

Abbreviations: ADT: androgen deprivation therapy; APA: apalutamide; IPCW: inverse probability of censoring weights; RPSFTM: rank preserving structural failure time model.

mHSPC

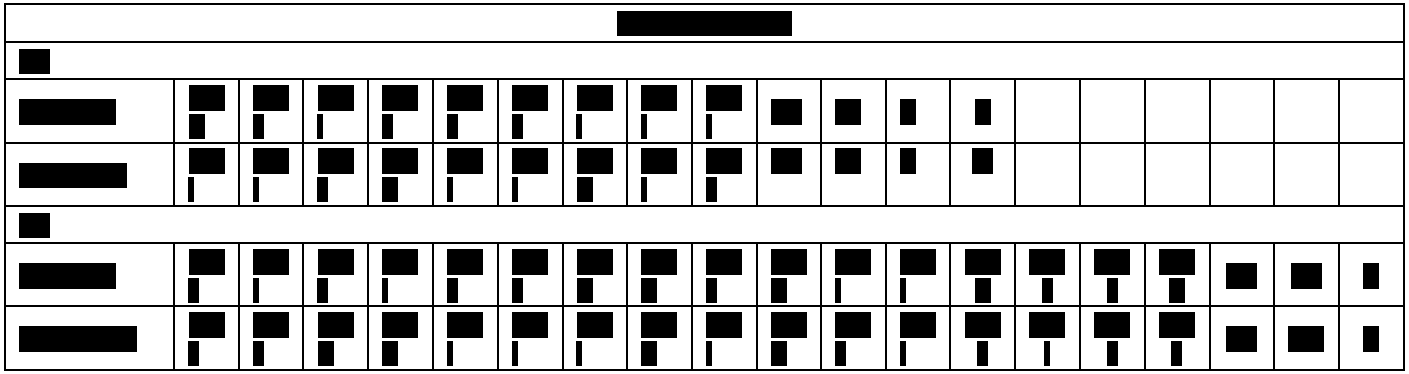
Figure 15 and Figure 16 present a comparison of the PFS2 and OS KM data from TITAN interim analysis 1 (IA1) and FA, which is presented in further detail in Section 7. The FA provides a substantial amount of additional follow-up and demonstrates a continued treatment effect of apalutamide plus ADT versus ADT alone over time.

Figure 15. Kaplan-Meier plot of PFS2 (TITAN IA1 vs final analysis)



Abbreviations: ADT: androgen deprivation therapy; APA: apalutamide.

Figure 16. Kaplan-Meier plot of OS (TITAN IA1 vs final analysis)



Abbreviations: ADT: androgen deprivation therapy; APA: apalutamide.

Figure 17 and Figure 18 present the PFS2 and OS KM data from TITAN FA that has been adjusted using the different methods outlined in Section 1. Six parametric distributions were fitted to each set of adjusted data from TITAN. However, given the results of the analysis are broadly consistent with the analyses presented previously using data from TITAN IA1, the unadjusted data has been maintained in the base-case analysis, with the adjusted data applied in scenario analysis for completeness. The extrapolated curves for the alternative scenarios are presented in Appendix A.

Figure 17. Kaplan-Meier plot of PFS2 (with additional crossover adjustment methods; TITAN final analysis)

Abbreviations: ADT: androgen deprivation therapy; APA: apalutamide; IPCW: inverse probability of censoring weights; RPSFTM: rank preserving structural failure time model.
Note: Unadjusted data includes deaths after switching to 2nd subsequent treatment

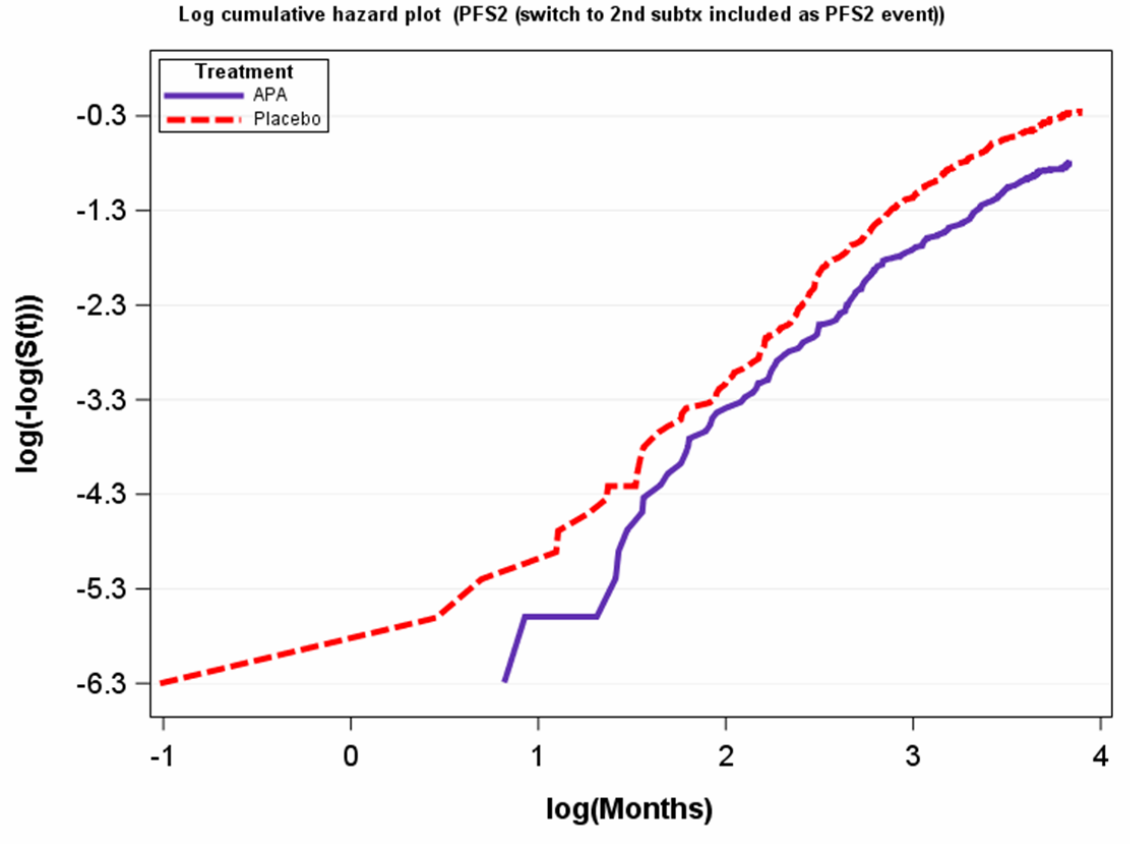
Figure 18. Kaplan-Meier plot of OS (with additional crossover adjustment methods; TITAN final analysis)

Abbreviations: ADT: androgen deprivation therapy; APA: apalutamide; IPCW: inverse probability of censoring weights; RPSFTM: rank preserving structural failure time model.

PFS2

Figure 19 presents the log-cumulative hazard plot of PFS2 from TITAN FA. The plot shows that the curves remained relatively parallel over time. Therefore, it was concluded that the proportional hazards assumption still holds, and it was considered appropriate to continue to apply jointly fitted models in the base case to make efficient use of the available data, using the ADT alone arm as the reference curve and the apalutamide plus ADT arm as a covariate. Note that these PFS2 data use different censoring rules to those specified in the TITAN protocol, See Appendix C for rationale and details.

Figure 19: Log cumulative hazard plot for unadjusted PFS2 in TITAN (Final analysis, clinical cut-off date 7 September 2020, ITT population)

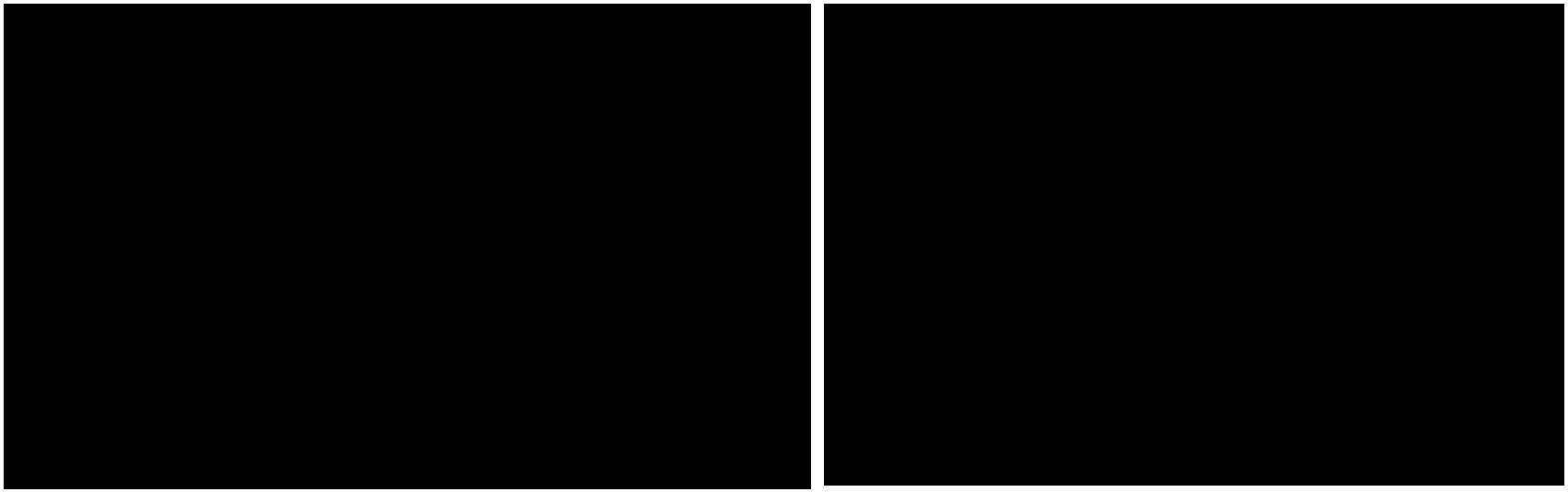


Abbreviations: PFS2: secondary progression-free survival.

Figure 20 presents the long-term PFS2 projections of the six parametric functions for the apalutamide plus ADT and ADT alone arms, with the goodness of fit statistics and landmark estimates over time presented in Table 33. As the updates to the model were being completed, an error

was identified in the formulae used to estimate some of the individual and jointly fitted Gompertz survival curves. Therefore, a correction has been applied to the model and all figures presented throughout the document include the corrected curves. This correction does not impact any of the base-case results.

Figure 20: Fitted parametric models (PFS2; TITAN final analysis) ADT alone (left) and apalutamide plus ADT (right)



Abbreviations: ADT: androgen deprivation therapy; APA: apalutamide; PFS2: secondary progression-free survival.

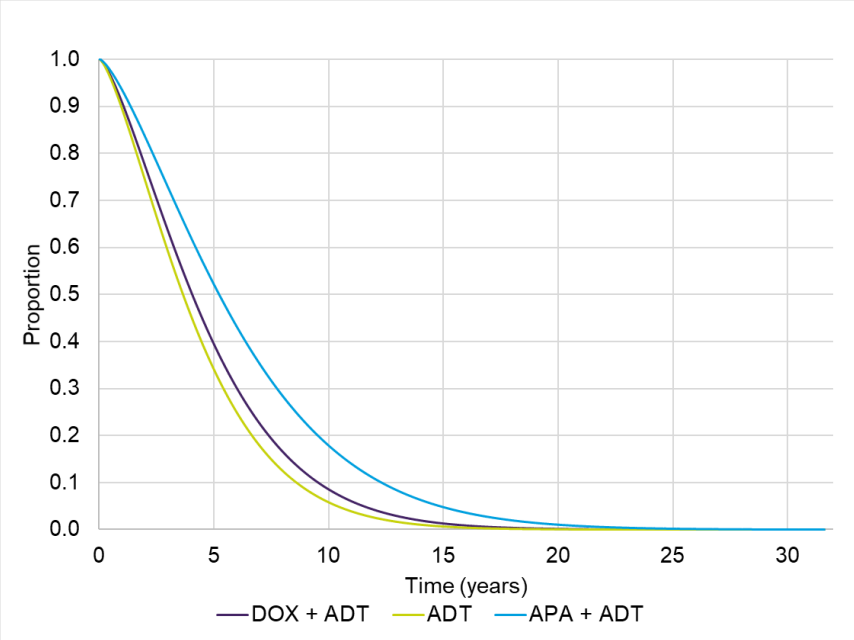
Table 33: Goodness-of-fit statistics and predicted survival (PFS2, TITAN final analysis)

	ADT alone						Apalutamide plus ADT					
	Weibull	Gompertz	Log-logistic	Log-normal	Generalized gamma	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalized gamma	Exponential
Statistical fit												
AIC	4492	4523	4479	4475	4476	4540	4492	4523	4479	4475	4476	4540
Rank	4	5	3	1	2	6	4	5	3	1	2	6
BIC	4507	4538	4494	4490	4496	4550	4507	4538	4494	4490	4496	4550
Rank	4	5	2	1	3	6	4	5	2	1	3	6
Predicted duration												
Median (months)	44	45	44	46	46	47	62	62	64	67	66	75
Mean (months)	52	48	73	79	72	68	74	64	99	107	100	105
Predicted survival per timepoint												
% at 5 years	34.0%	33.9%	37.9%	40.9%	39.7%	41.4%	52.1%	51.7%	52.7%	54.0%	53.6%	57.5%
% at 10 years	5.8%	1.9%	16.6%	19.8%	17.4%	17.1%	17.8%	8.8%	26.6%	30.2%	28.3%	33.1%
% at 20 years	0.1%	0.0%	6.1%	7.1%	5.0%	2.9%	1.1%	0.0%	10.6%	12.8%	10.4%	10.9%
% at 30 years	0.0%	0.0%	3.2%	3.4%	1.9%	0.5%	0.0%	0.0%	5.8%	6.7%	4.7%	3.6%

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

The Weibull curve is maintained in the base case analysis as it provides long-term projections that are consistent with feedback from UK clinical experts and with the curves selected for both PFS and OS, which avoids the potential issue of the curves crossing over time. Consistent with the original submission, as PFS2 data were not available for docetaxel plus ADT, the hazard ratio for PFS was applied as a proxy to estimate the docetaxel + ADT extrapolation. Figure 21 presents the updated base-case PFS2 extrapolations when the data from TITAN FA is used.

Figure 21: PFS2 docetaxel plus ADT vs apalutamide plus ADT and ADT alone

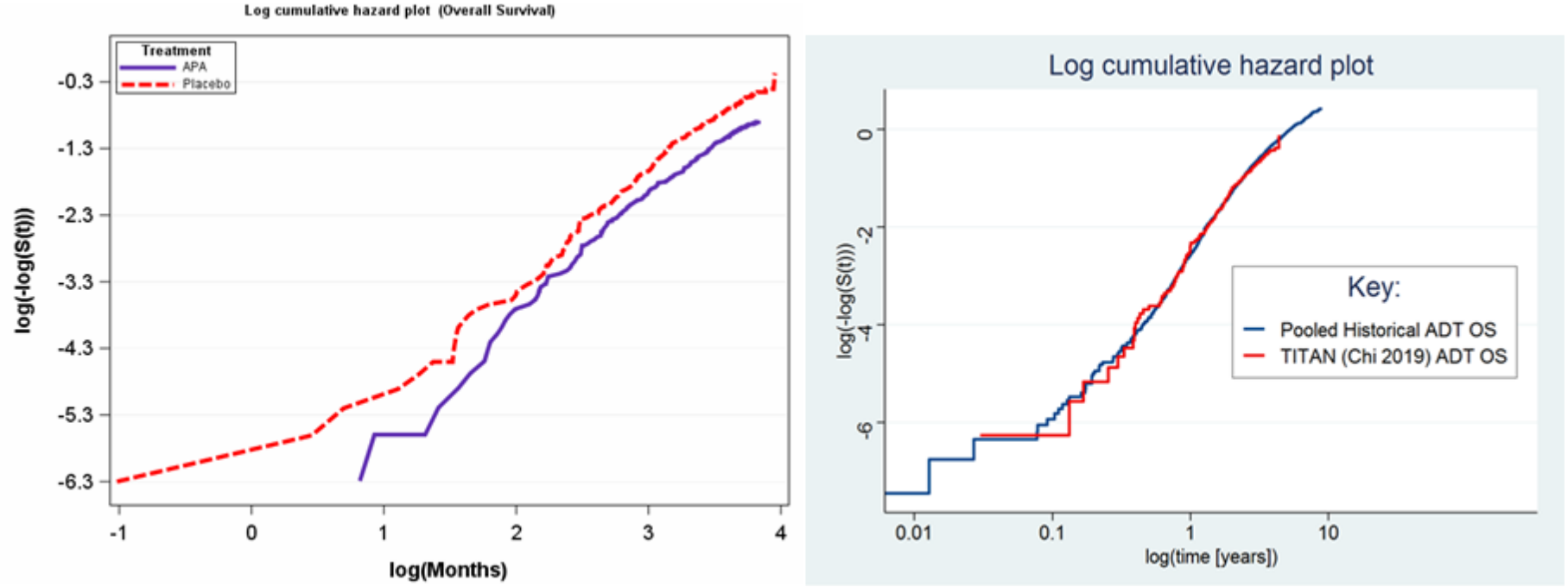


Abbreviations: ADT: androgen deprivation therapy; APA: apalutamide; Dox, docetaxel.

OS

Although TITAN FA significantly increases the maturity of the OS data, it still remains that there is a significant amount of historical ADT OS data available from the literature that provide longer follow-up relative to TITAN. Therefore, the informed fits approach was maintained in the base-case analysis to reduce uncertainty in the long-term survival projections. Figure 22 presents the log-cumulative hazard plots for apalutamide plus ADT versus ADT alone from TITAN, and ADT alone from TITAN versus the pooled historical ADT data. Given the curves remain parallel over time this demonstrates that the assumption of common shape between the curves required for the informed fits analysis to be considered appropriate still holds. This is supported by the Schoenfeld residuals plot which provides a p value of p=0.7169.

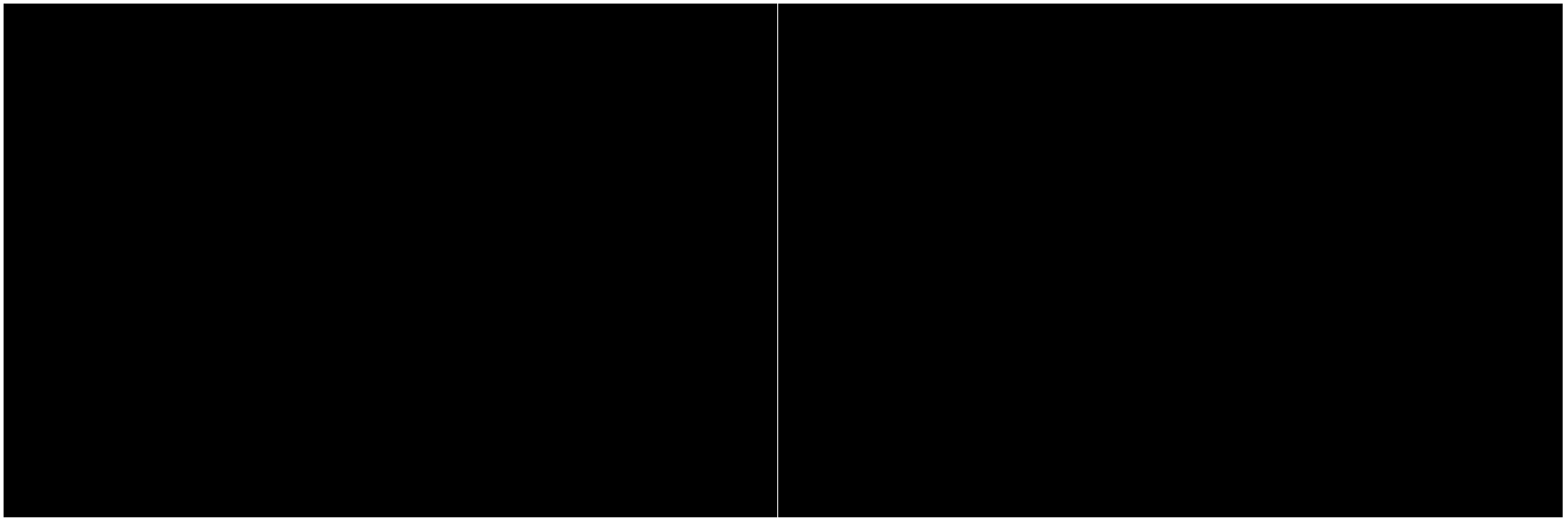
Figure 22: Log-cumulative hazard plots (overall survival: TITAN apalutamide plus ADT vs ADT alone, and TITAN ADT alone vs pooled historical ADT)



Abbreviations: ADT: androgen deprivation therapy; OS: overall survival

Six parametric functions were fitted to the OS data for each treatment arm from the TITAN trial. Figure 23 presents the long-term projections of the six parametric functions for OS for the ADT alone and apalutamide plus ADT arms. Summaries of the goodness-of-fit statistics and survival estimates over time are also presented in Table 34

Figure 23: Fitted parametric models (OS informed fits; TITAN): ADT alone (left) and apalutamide plus ADT (right)



Abbreviations: ADT: androgen deprivation therapy; APA: apalutamide; OS: overall survival.

Table 34: Goodness-of-fit statistics and predicted survival (OS, TITAN final analysis)

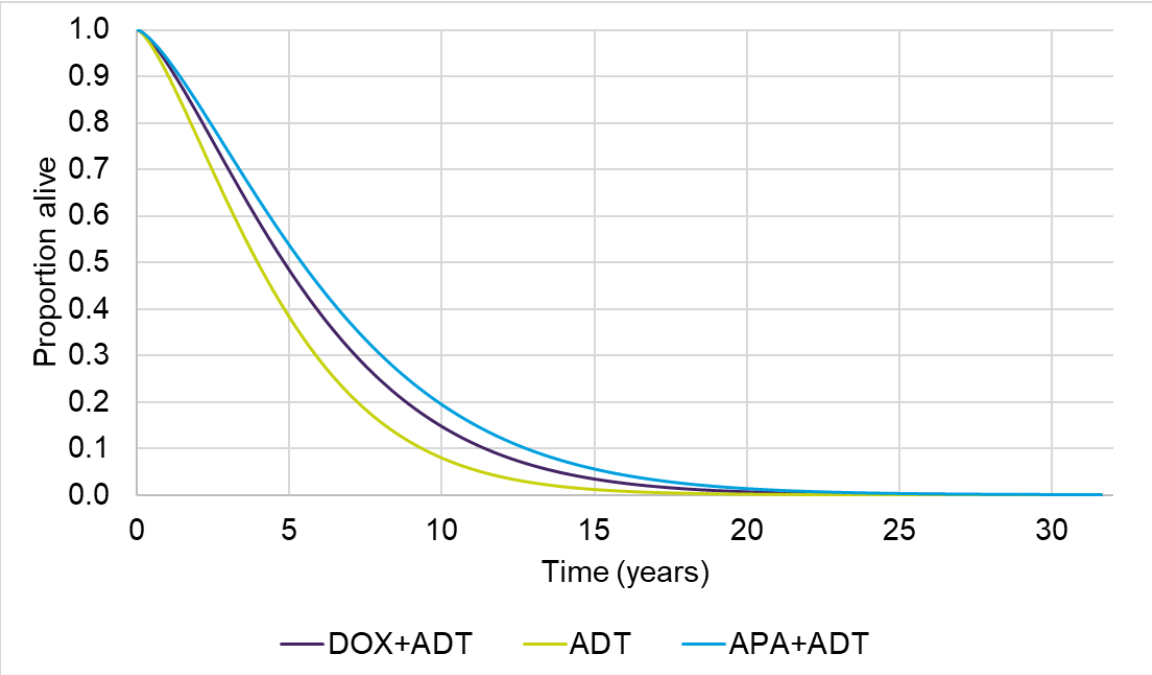
	ADT alone						Apalutamide plus ADT					
	Weibull	Gompertz	Log-logistic	Log-normal	Generalized gamma	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalized gamma	Exponential
Statistical fit												
AIC	8840	9002	8758	8891	8790	9089	8840	9002	8758	8891	8790	9089
Rank	3	5	1	4	2	6	3	5	1	4	2	6
BIC	8866	9027	8784	8916	8822	9109	8866	9027	8784	8916	8822	9109
Rank	3	5	1	4	2	6	3	5	1	4	2	6
Predicted duration												
Median (months)	47	49	47	50	48	52	65	67	64	69	65	78
Mean (months)	56	55	74	82	64	74	77	72	96	107	86	109
Predicted survival per timepoint												
% at 5 years	38.0%	40.2%	39.6%	43.2%	39.8%	44.8%	53.5%	55.0%	52.8%	55.1%	53.8%	58.7%
% at 10 years	7.9%	6.8%	16.4%	20.9%	13.2%	20.1%	19.3%	17.2%	25.1%	30.5%	23.8%	34.4%
% at 20 years	0.1%	0.0%	5.5%	7.4%	1.7%	4.0%	1.3%	0.0%	9.1%	12.5%	5.0%	11.9%
% at 30 years	0.0%	0.0%	2.8%	3.4%	0.3%	0.8%	0.0%	0.0%	4.7%	6.4%	1.2%	4.1%

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

The Weibull curves are maintained in the base case analysis as they provide clinically plausible long-term projections that continue to be consistent with the expectation of clinical expert opinion sought by both the company and the ERG.

Figure 23 presents the updated base-case OS extrapolations when the data from TITAN FA is used. To estimate OS for docetaxel plus ADT, HRs derived from the Bayesian NMA for docetaxel plus ADT versus apalutamide plus ADT which have been updated with data from TITAN FA were applied to the selected OS curve for apalutamide plus ADT. As detailed in Section 8, the mean HR for OS was 0.855 which has decreased slightly compared to the previous HR estimated using data from TITAN IA1 of 0.88. The resulting OS curves for docetaxel plus ADT compared to apalutamide plus ADT and ADT alone are presented in Figure 24.

Figure 24: OS docetaxel plus ADT vs apalutamide plus ADT and ADT alone



Abbreviations: ADT: androgen deprivation therapy; APA: apalutamide; Dox, docetaxel.

9.2. Additional updates from TITAN FA

Additional EQ-5D-5D data was collected as part of the TITAN FA which has been used to update the existing utility regression models. All observations with missing data were excluded from the analyses, as well as all observations obtained after treatment switching. Figure 25 presents the mean utility score over time for apalutamide plus ADT and placebo plus ADT for all recorded observations. The variation in mean utility towards the end of the trial follow-up is caused by the reduction in the number completed questionnaires over time (Appendix B).

Figure 25: Mean utility reported in each cycle

Table 35 presents a comparison of the utility regression model applied in the model using data from IA1 to the final analysis data-cut. Radiographic progression and the impact of adverse events remained statistically significant covariates when tested in univariate analysis (p value < 0.001), and the regression coefficients demonstrate that each of these variables are still estimated as have a meaningful impact on HRQL.

Table 35: Utility regression output (IA1 vs final analysis)

Coefficient	IA1	Final analysis
Intercept	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]
rPFS	[redacted]	[redacted]
Abbreviations: rPFS, radiographic progression free survival.		

To estimate the impact of AEs on HRQoL in the model, updated rates of patients experiencing grade at least one 3/4 AE from TITAN FA summarised in Table 36 were applied. The equivalent rate for docetaxel was updated using the odds ratio estimated for Grade 3/4 AEs from the safety NMA presented in Section 8 The odds ratio estimated using TITAN FA was [redacted] compared with the previous odds ratio of [redacted] estimating using data from TITAN A1.

Table 36: Proportion of patients experiencing a Grade 3/4 adverse event

Treatment	TITAN IA1 (median follow-up)	TITAN FA (median follow-up
Apalutamide plus ADT	[redacted]	[redacted]
ADT alone	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy.

The updated frequencies of each adverse event which are used to calculate adverse event management costs are summarised in Table 37.

Table 37: Adverse events incidence

Adverse event	Anaemia	Asthenia	Diarrhoea	Fall	Febrile neutropenia	Fracture	Hypertension	Hypothyroidism	Neutropenia	Rash	Thrombocytopenia	Source
mHSPC (TITAN IA1)												
Apalutamide plus ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TITAN IA1
ADT alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TITAN IA1
mHSPC (TITAN FA)												
Apalutamide plus ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TITAN FA
ADT alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TITAN FA

Abbreviations: ADT: androgen deprivation therapy; mHSPC: metastatic hormone-sensitive prostate cancer.

9.3. Updated results - nmHRPC

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

The results of the original submitted company base-case analysis, with the correction of errors identified by the ERG included (summarised in Section 5.3.2 in the ERG report) are presented in Table 38. The individual impact on the results of the assumptions applied in the ERG base-case analysis and the new scenario analysis presented by the company are also presented.

Table 38: Scenario analysis results (nmHRPC, including [redacted])

Scenario	ICER vs ADT alone
Original company base-case ICER (including correction of errors identified by the ERG)	Dominates
1. Company scenario: PFS2 and OS curves: RPFSTM (COU-AA-302 IA3 data-cut)	Dominates
2. ERG scenario: OS extrapolation - jointly fitted generalised gamma	Dominates
3. ERG scenario: Unadjusted duration of mHRPC health states	Dominates
4. ERG scenario: Mean health state duration for 3L based on the active treatment and BSC durations from TA387	Dominates
5. ERG scenario: Unadjusted health state utilities for 2L/3L mHRPC	Dominates
6. ERG scenario: Duration of AE disutilities in the pre progression health state – 2 weeks	Dominates
7. ERG scenario: Neutropenia cost – £150.16	Dominates
8. ERG scenario: Resource use based on the ERG's clinical advice	Dominates
9. ERG scenario: Exclude unscheduled MRU costs	Dominates
ERG base-case	Dominates

Abbreviations: 2L: second line, 3L: third line; ADT: androgen deprivation therapy; AE: adverse event; BSC: best supportive care; ERG: evidence review group; ICER: incremental cost-effectiveness ratio; mHRPC: metastatic hormone relapsed prostate cancer; MRU: medical resource use; OS: overall survival; PFS2: second progression free survival; QALY: quality-adjusted life-years; RPSFTM: rank preserving structural failure time model.

Following feedback from the ERG, the original submitted company base-case has been revised to address some of the key issues raised. All assumptions included in the ERG's base-case have been incorporated in the revised company base-case with one exception. The ERG

scenario where the utilities for the 2L/3L mHRPC health state have been calculated using the values from TA387 without any adjustment has not been applied for the reasons outlined in the response to Issue 4 in the technical engagement response.

The results of the revised company base-case are presented in Table 39.

Table 39: Revised company base-case results, nmHRPC, apalutamide plus ADT vs ADT alone including [redacted]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ADT alone	[redacted]	5.50	[redacted]				
Apalutamide plus ADT	[redacted]	6.26	[redacted]	[redacted]	0.76	[redacted]	Dominates

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

9.4. Updated results - mHSPC

The result of the original submitted company base-case analysis (with the correction of errors identified by the ERG included) and the impact on the results of using the TITAN FA is presented in Table 40. The individual impact on the results of the assumptions applied in the ERG base-case analysis and the new scenario analysis presented by the company is presented in Table 41.

Table 40: Original base-case results including TITAN FA including [redacted] (mHSPC)

Scenario	ICER vs ADT alone	ICER vs docetaxel + ADT	Weighted ICER (73% ADT alone vs (27% docetaxel + ADT)

Original company base-case (including correction of errors identified by the ERG): TITAN IA1	£11,265	£8,758	£10,588
Original company base-case (including correction of errors identified by the ERG): TITAN FA	Dominates	Dominates	Dominates

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio.

Table 41: Scenario analysis results (mHSPC) including [redacted]

Scenario	ICER vs ADT alone	ICER vs docetaxel + ADT	Weighted ICER (73% ADT alone vs (27% docetaxel + ADT)
Original company base-case ICER (including correction of errors identified by the ERG): TITAN FA	Dominates	Dominates	Dominates
1. PFS2 and OS curves (unstratified, unadjusted)	Dominates	Dominates	Dominates
2. Company scenario: PFS2 and OS curves: RPFSTM (COU-AA-302 FA data-cut)	£3,903	Dominates	Dominates
3. Company scenario: PFS2 and OS curves: RPFSTM (COU-AA-302 IA3 data-cut)	£3,891	Dominates	Dominates
4. ERG scenario: Unadjusted duration of mHRPC health states	Dominates	Dominates	Dominates
5. ERG scenario: Mean health state duration for 3L based on the active treatment and BSC durations from TA387	Dominates	Dominates	Dominates
6. ERG scenario: Unadjusted health state utilities for 2L/3L	Dominates	Dominates	Dominates
7. ERG scenario: Duration of AE disutilities in the pre progression health state – 2 weeks	Dominates	Dominates	Dominates
8. ERG scenario: Duration of AE costs for docetaxel – 6 months	Dominates	Dominates	Dominates
9. Company scenario: updated docetaxel adverse event approach	Dominates	Dominates	Dominates
10. ERG scenario: Neutropenia cost – £150.16	Dominates	Dominates	Dominates
11. ERG scenario: Resource use based on the ERG's clinical advice	Dominates	Dominates	Dominates
12. ERG scenario: Exclude unscheduled MRU costs	Dominates	Dominates	Dominates
ERG base-case	Dominates	Dominates	Dominates

Abbreviations: 2L: second line, 3L: third line; ADT: androgen deprivation therapy; AE: adverse event; APA: apalutamide; BSC: best supportive care; ERG: evidence review group; ICER: incremental cost-effectiveness ratio; IPCW: inverse probability of censoring weights; mHRPC: metastatic hormone relapsed prostate cancer; MRU: medical resource use; OS: overall survival; PFS2: secondary progression free survival; QALY: quality-adjusted life-years; RPSFTM: rank preserving structural failure time model.

Following feedback from the ERG, the original submitted company base-case has been revised to address some of the key issues raised. All assumptions included in the ERG's base-case have been incorporated in the revised company base-case with only two exceptions. Firstly, the ERG scenario where the utilities for the 2L/3L mHRPC health state have been calculated using the values from TA387 without any adjustment has not been applied for the reasons outlined in the response to Issue 4 in the technical engagement response. Secondly, the ERG scenario which only applies adverse event management costs associated with docetaxel + ADT for six months has been amended for the reasons outlined in the response to Issue 6 in the technical engagement response.

The results of the revised company base-case are presented in Table 42 to Table 44.

Table 42: Revised company base-case, mHSPC, fully incremental results for docetaxel eligible patients including [redacted]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Apalutamide plus ADT	[redacted]	6.375	[redacted]				
ADT alone	[redacted]	4.664	[redacted]	[redacted]	-1.711	[redacted]	Dominated
Docetaxel plus ADT	[redacted]	5.698	[redacted]	[redacted]	1.034	[redacted]	£10,482

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life year gain; QALYs: quality-adjusted life years

Table 43: Revised company base-case results, mHSPC, docetaxel ineligible patients including [redacted]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ADT alone	[redacted]	4.66	[redacted]				
Apalutamide plus ADT	[redacted]	6.38	[redacted]	[redacted]	1.71	[redacted]	Dominates

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

Table 44: Revised company base-case results, mHSPC, apalutamide plus ADT vs weighted comparator (73% ADT alone, 27% docetaxel plus ADT) including [redacted]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Weighted comparator	[redacted]	4.94	[redacted]				
Apalutamide plus ADT	[redacted]	6.38	[redacted]	[redacted]	1.43	[redacted]	Dominates

Abbreviations: ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

9.5. Interpretation and conclusions of economic evidence

The additional survival analyses presented for both the nmHRPC and mHSPC indications demonstrate that the results are consistent regardless of level of crossover present in COU-AA-302 data used to adjust for second novel therapy use. Additionally, for the mHSPC indication, the data from TITAN FA provides a substantial amount of additional follow-up which reduces the uncertainty in the long-term survival projections, with the results demonstrating a continued treatment effect of apalutamide plus ADT versus ADT alone over time.

Across both indications, the results of the cost-effectiveness analysis demonstrate that treatment with apalutamide plus ADT can be considered a cost-effective use of NHS resources when the updated confidential PAS is applied. For the nmHRPC indication apalutamide plus ADT is cost-effective against ADT while for the mHSPC indication it can be considered to be a cost-effective therapy when considering the entire mHSPC patient population.

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

nmHRPC: Including [redacted]

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Original company base-case ICER (including correction of errors identified by the ERG in Section 5.3.2 of the ERG report)			Dominates
ERG base-case (Section 4.2.7 of the ERG report): Extrapolation of OS for nmHRPC	Weibull	generalised gamma	Dominates
ERG base-case (Section 4.2.8.3 of the ERG report): Mean health state durations of first, second and third line mHRPC health states	Adjusted to account for patients who died pre-progression	No adjustment	Dominates
ERG base-case (Section 4.2.11.4 of the ERG report): Mean health state duration of third line mHRPC	Duration of third line mHRPC based on the time spent in the active treatment state from NICE TA387	Duration of third line mHRPC based on the time spent in both active treatment and best supportive care from NICE TA387	Dominates
ERG base-case (Section 4.2.10 of the ERG report): Duration of adverse event disutilities in the pre-progression health state	Disutilities applied for the duration of the pre-progression health state	Disutilities applied for two weeks	Dominates

ERG base-case (Section 4.2.11 of the ERG report): Neutropenia cost	£862.79	£150,16	Dominates
ERG base-case (Section 4.2.11 of the ERG report): Resource use	Based on the Company's clinical advice	Based on the ERG's clinical advice	Dominates
ERG base-case (Section 4.2.11 of the ERG report): Unscheduled medical resource use costs	Include unscheduled medical resource use costs	Exclude unscheduled medical resource use costs	Dominates
Company's preferred base case following technical engagement			Incremental QALYs: [redacted] Incremental costs: [redacted] ICER: Dominates

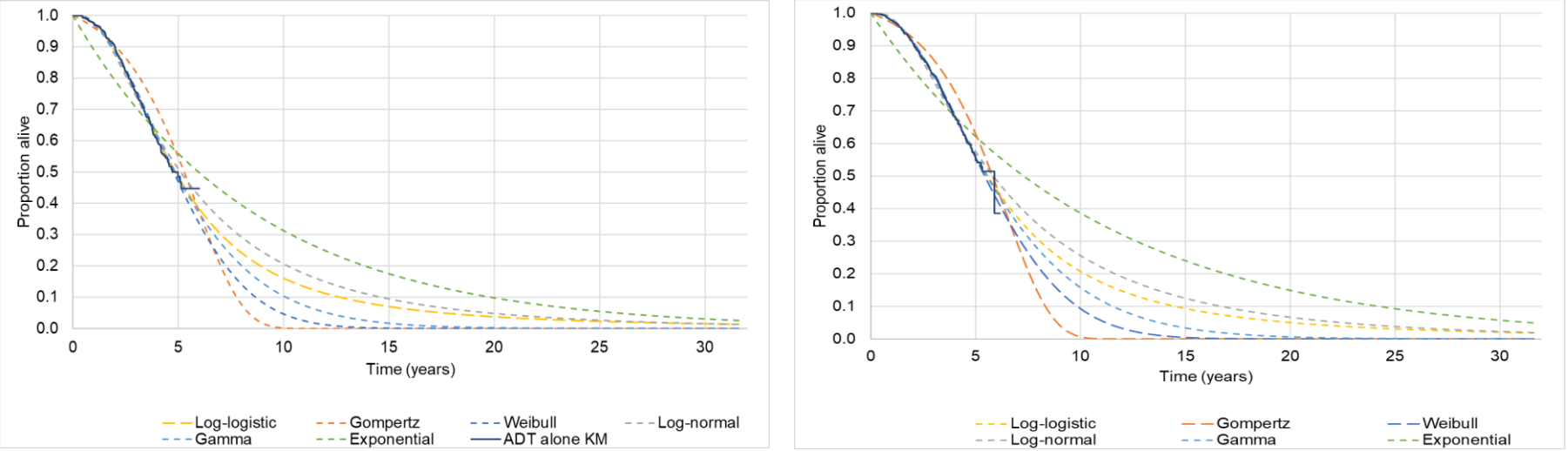
mHSPC Including [redacted]

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER vs ADT alone	Impact on the company's base-case ICER vs docetaxel + ADT	Impact on the company's base-case ICER: weighted comparator (73% ADT alone vs 27% docetaxel + ADT)
Original company base-case: (including TITAN FA and correction of errors identified by the ERG in Section 5.3.2 of the ERG report)			Dominates	Dominates	Dominates
ERG base-case (Section 4.2.8.3 of the ERG report): Mean health state durations of first, second and third line mHRPC health states	Adjusted to account for patients who died pre-progression	No adjustment	Dominates	Dominates	Dominates
ERG base-case (Section 4.2.11.4 of the ERG report): Mean health state duration of third line mHRPC	Duration of third line mHRPC based on the time spent in the active treatment state from NICE TA387	Duration of third line mHRPC based on the time spent in both active treatment and best supportive care from NICE TA387	Dominates	Dominates	Dominates
ERG base-case (Section 4.2.10 of the ERG report): Duration of adverse event disutilities in the pre-progression health state	Disutilities applied for the duration of the pre-progression health state	Disutilities applied for two weeks	Dominates	Dominates	Dominates

New company scenario (Issue 6 of the technical engagement response: Duration of adverse event costs for docetaxel (mHSPC)	Adverse event management costs associated with docetaxel applied throughout the pre-progression health state	Adverse event costs associated with docetaxel applied for six months (including updated adverse event rates using real world evidence) and costs associated with ADT alone applied thereafter	Dominates	Dominates	Dominates
ERG base-case (Section 4.2.11 of the ERG report): Neutropenia cost	£862.79	£150,16	Dominates	Dominates	Dominates
ERG base-case (Section 4.2.11 of the ERG report): Resource use	Based on the Company's clinical advice	Based on the ERG's clinical advice	Dominates	Dominates	Dominates
ERG base-case (Section 4.2.11 of the ERG report): Unscheduled medical resource use costs	Include unscheduled medical resource use costs	Exclude unscheduled medical resource use costs	Dominates	Dominates	Dominates
Company's preferred base case following technical engagement			Incremental QALYs: [redacted] Incremental costs: [redacted] ICER: Dominates	Incremental QALYs: [redacted] Incremental costs: [redacted] ICER: Dominates	Incremental QALYs: [redacted] Incremental costs: [redacted] ICER: Dominates

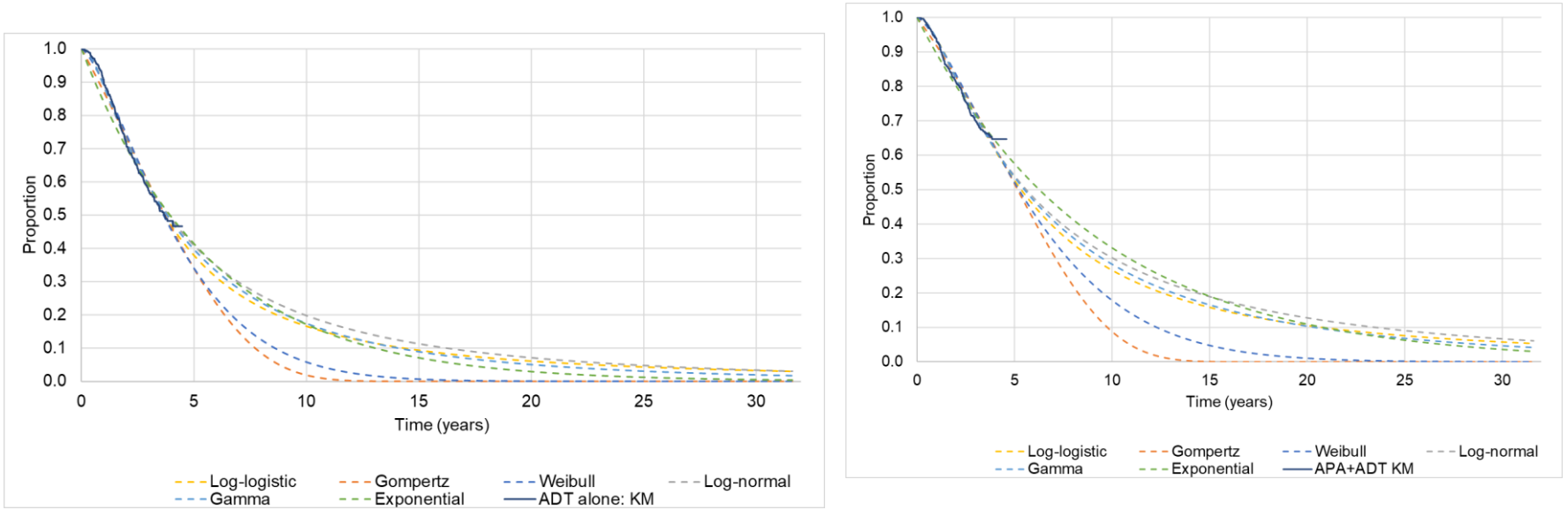
Appendix A

Figure 26. Jointly fitted parametric models (OS adjusted using RPFSTM COU-AA-302 IA3; SPARTAN final analysis) ADT alone (left) and apalutamide plus ADT (right)



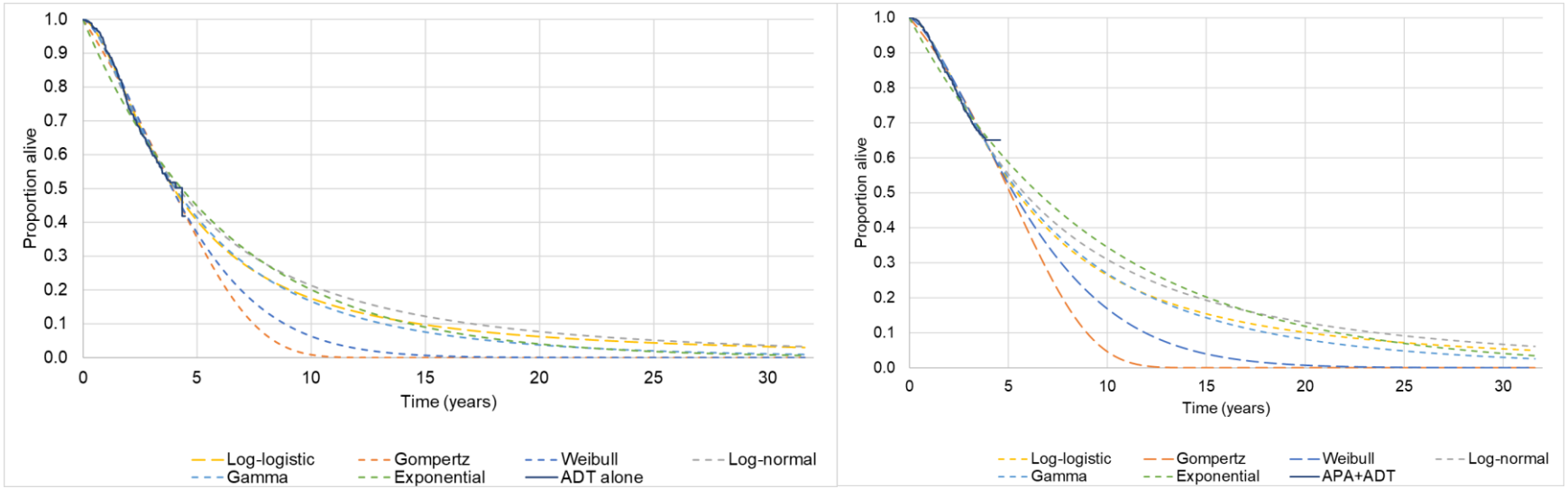
Abbreviations: ADT: androgen deprivation therapy; APA: apalutamide; PFS2: secondary progression-free survival.

Figure 27. Jointly fitted parametric models (PFS2 unadjusted; TITAN final analysis) ADT alone (left) and apalutamide plus ADT (right)



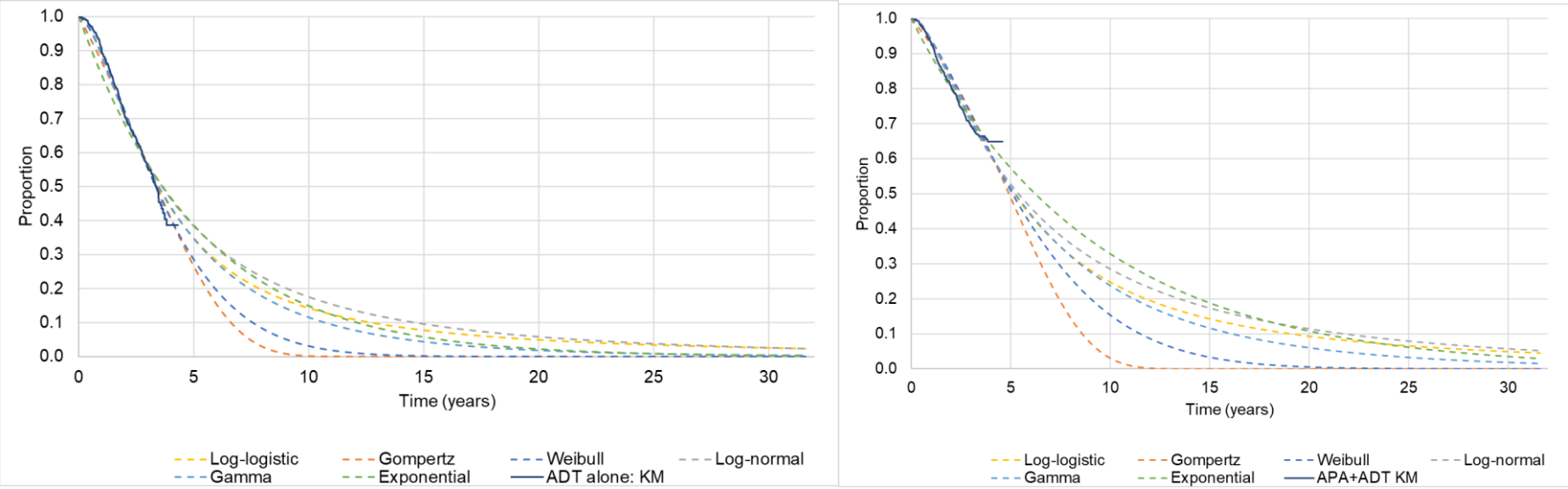
Abbreviations: ADT: androgen deprivation therapy; APA: apalutamide; PFS2: secondary progression-free survival.

Figure 28. Jointly fitted parametric models (OS unadjusted; TITAN final analysis) ADT alone (left) and apalutamide plus ADT (right)



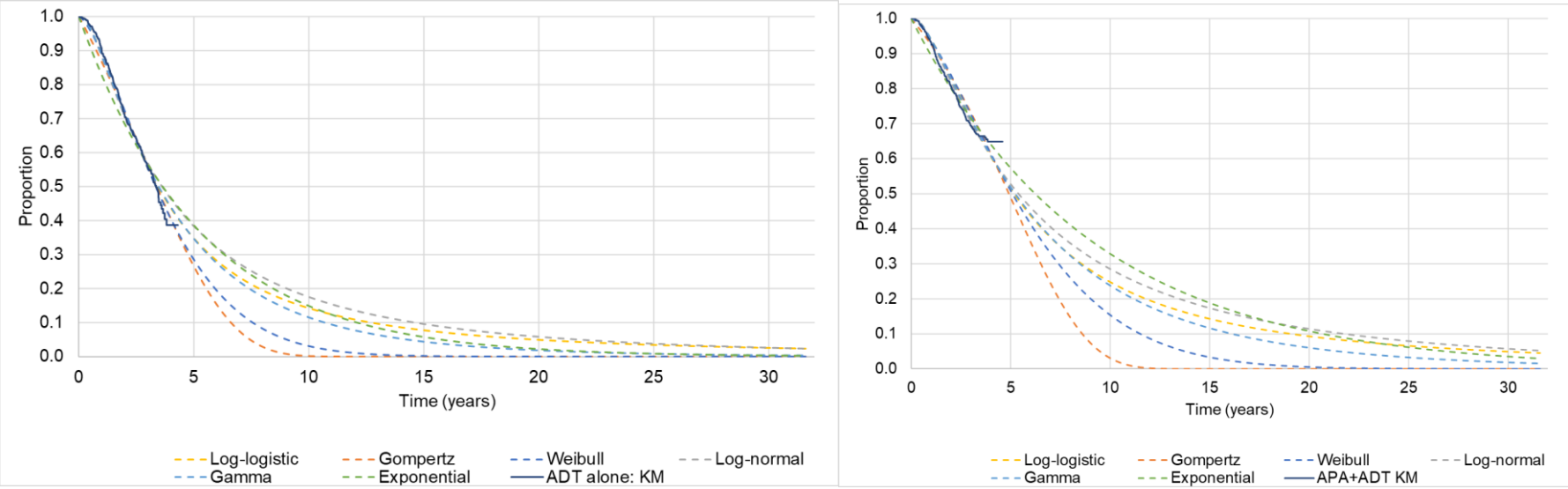
Abbreviations: ADT: androgen deprivation therapy; APA: apalutamide; PFS2: secondary progression-free survival.

Figure 29. Jointly fitted parametric models (PFS2 adjusted using RPFSTM COU-AA-302 FA; TITAN final analysis) ADT alone (left) and apalutamide plus ADT (right)



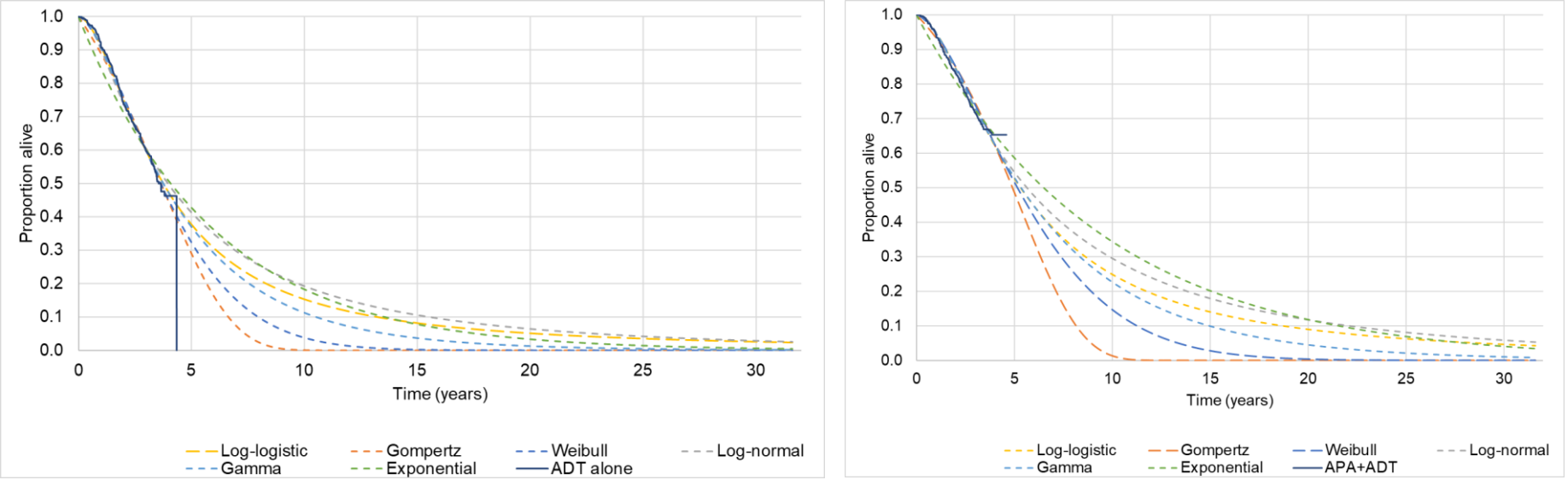
Abbreviations: ADT: androgen deprivation therapy; APA: apalutamide; PFS2: secondary progression-free survival.

Figure 30. Jointly fitted parametric models (OS adjusted using RPFSTM COU-AA-302 FA; TITAN final analysis) ADT alone (left) and apalutamide plus ADT (right)



Abbreviations: ADT: androgen deprivation therapy; APA: apalutamide; PFS2: secondary progression-free survival.

Figure 31. Jointly fitted parametric models (OS adjusted using RPFSTM COU-AA-302 IA3; TITAN final analysis) ADT alone (left) and apalutamide plus ADT (right)



Abbreviations: ADT: androgen deprivation therapy; APA: apalutamide; PFS2: secondary progression-free survival.

Appendix B

Table 45: Results of Descriptive Analyses of Utility Data (TITAN final analysis)

Visit	Tx	n	Mean	SD	Min	Q1	Median	Q3	Max
Baseline	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Visit	Tx	n	Mean	SD	Min	Q1	Median	Q3	Max
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 1	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 2	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 7	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Visit	Tx	n	Mean	SD	Min	Q1	Median	Q3	Max
Cycle 8	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 10	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 12	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 14	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 15	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Visit	Tx	n	Mean	SD	Min	Q1	Median	Q3	Max
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Cycle 16	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Cycle 17	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 18	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Cycle 19	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Cycle 22	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Cycle 23	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Visit	Tx	n	Mean	SD	Min	Q1	Median	Q3	Max
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Cycle 24	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Cycle 25	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Cycle 26	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Cycle 27	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 28	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 29	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 30	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Visit	Tx	n	Mean	SD	Min	Q1	Median	Q3	Max
Cycle 31	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 32	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Cycle 33	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 34	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Cycle 35	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Cycle 36	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 37	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Cycle 39	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Visit	Tx	n	Mean	SD	Min	Q1	Median	Q3	Max
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	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	PLA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 43	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EOT	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4mfu	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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8mfu	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12mfu	Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	APA+ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLE Cycle 1	*APA+ADT*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Visit	Tx	n	Mean	SD	Min	Q1	Median	Q3	Max
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OLE Cycle 3	*APA+ADT*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLE Cycle 4	*APA+ADT*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLE Cycle 5	*APA+ADT*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLE Cycle 6	*APA+ADT*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLE Cycle 7	*APA+ADT*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLE Cycle 8	*APA+ADT*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLE Cycle 9	*APA+ADT*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLE Cycle 10	*APA+ADT*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLE Cycle 11	*APA+ADT*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLE Cycle 12	*APA+ADT*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLE Cycle 13	*APA+ADT*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLE Cycle 14	*APA+ADT*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLE Cycle 15	*APA+ADT*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLE Cycle 16	*APA+ADT*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLE Cycle 17	*APA+ADT*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLE Cycle 18	*APA+ADT*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLE Cycle 19	*APA+ADT*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADT: androgen deprivation therapy; APA: apalutamide; EOT: end of treatment; OLE: open label extension; Q1: first quartile; Q3: third quartile; PLA: placebo; SD: standard error; Tx: treatment; 4mfu: 4-months follow-up; 8mfu: 8-months follow-up; 12mfu: 12-months follow-up.

Appendix C

Switching patterns in TITAN FA

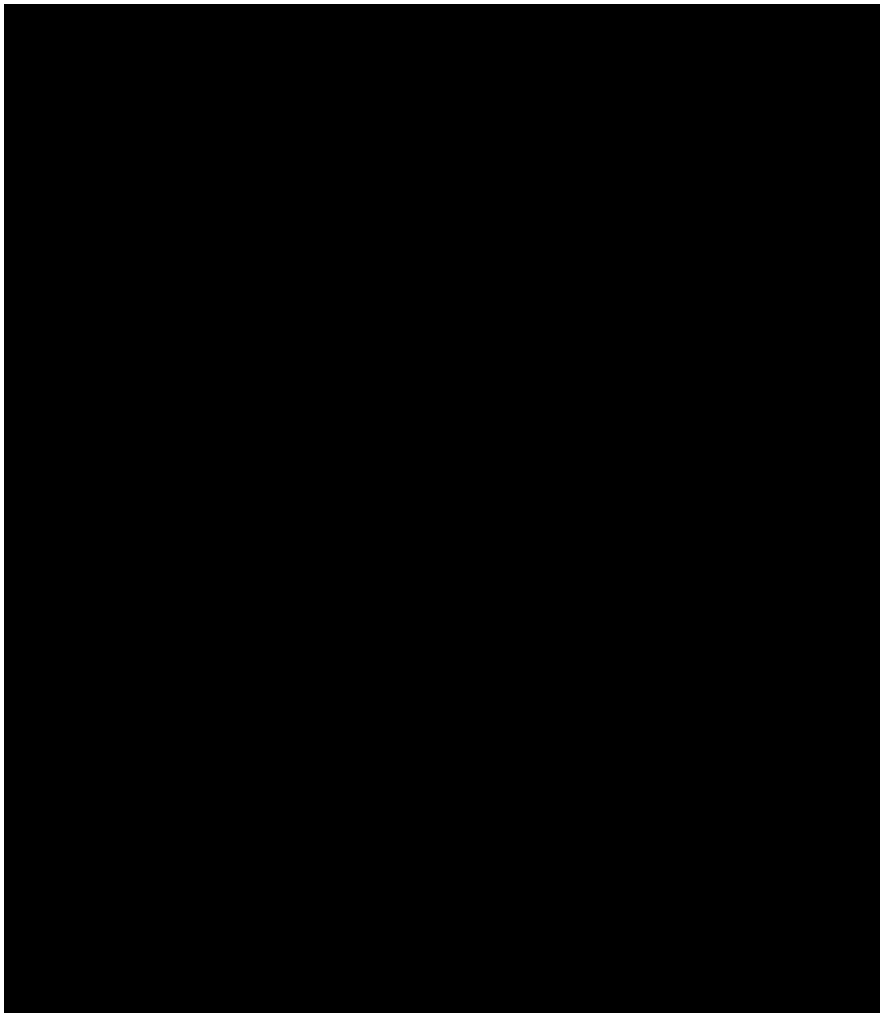
Based on the final analysis (FA; clinical cut-off date 7th September 2020) of TITAN, [redacted] patients in the ADT arm ([redacted]% of the randomized subjects) either received both abiraterone acetate and enzalutamide as subsequent therapy, or crossed over to the apalutamide plus ADT arm (Table 46). [redacted] patients in the APA arm ([redacted]% of the randomized subjects) received either of the therapies with the majority receiving abiraterone acetate. Figure 32 and Figure 33: show the pathway of the patients who received subsequent novel therapies not in line with UK restrictions. Subsequent therapies considered as life-prolonging are shown in Table, with docetaxel and abiraterone acetate plus prednisone the most frequently administered as a subsequent therapy.

Table 46: Summary of subsequent therapy for prostate cancer (TITAN FA, clinical cut-off date 7 September 2020)

	Placebo plus ADT (n=527)	Apalutamide plus ADT (n=525)
Number of subjects alive at treatment discontinuation (denominator for table below)	[redacted]	[redacted]
Number of subjects with selected subsequent therapy for prostate cancer	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]
Abiraterone	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]
Cabazitaxel	[redacted]	[redacted]
Radium 223	[redacted]	[redacted]
Sipuleucel-T	[redacted]	[redacted]
Cabazitaxel Acetone	[redacted]	[redacted]

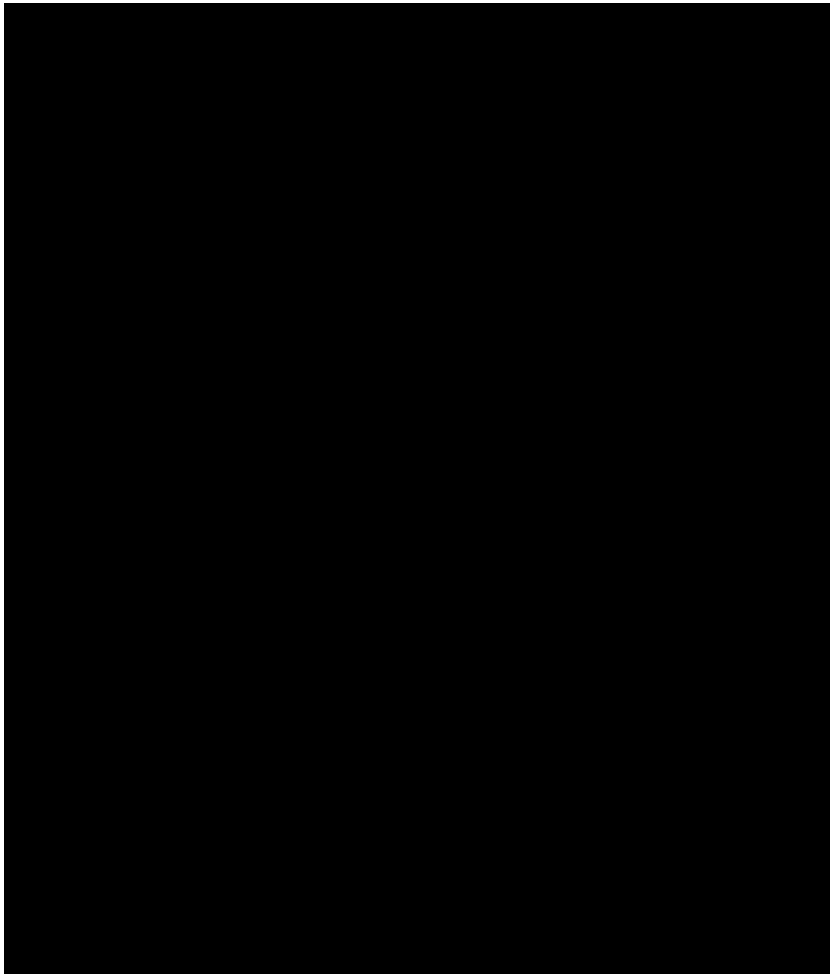
Note: table taken from TITAN CSR, patients could receive more than one subsequent treatment

Figure 32: Pathway plots of the [redacted] apalutamide patients that received 2 novel therapies at FA (TITAN)



Abbreviations: PD: Progressive disease; PFS2: Progression-free Survival on First Subsequent treatment; SubTX: Subsequent therapy.

Figure 33. Pathway plots of the [redacted] Placebo patients that either received 2 novel therapies or crossed over to the apalutamide arm at FA (TITAN)



Abbreviations: AA, abiraterone acetate; APA, apalutamide; ENZA, enzalutamide; PD: Progressive disease; PFS2: Progression-free Survival on First Subsequent treatment; SubTX: Selected Subsequent therapy

Figure 34 and Figure 35 show the treatment patterns over time for each patient included in the apalutamide plus ADT and placebo plus ADT arms. They demonstrate that time between progression and/or discontinuation of randomized treatment to switch was highly variable in the ADT arm.

Figure 34: Treatment timeline by patient from baseline (apalutamide plus ADT), TITAN FA

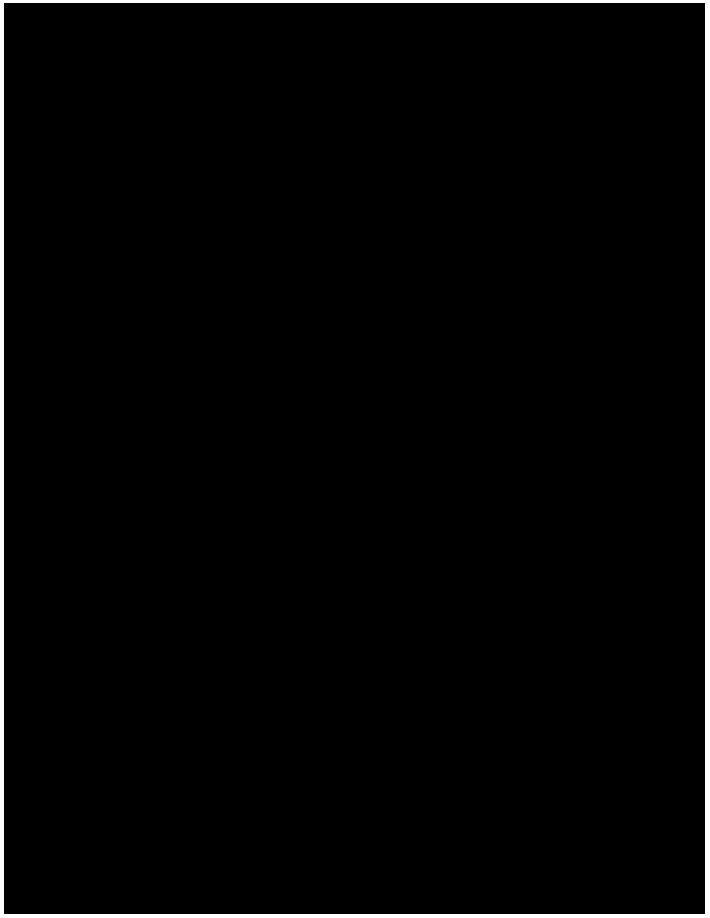
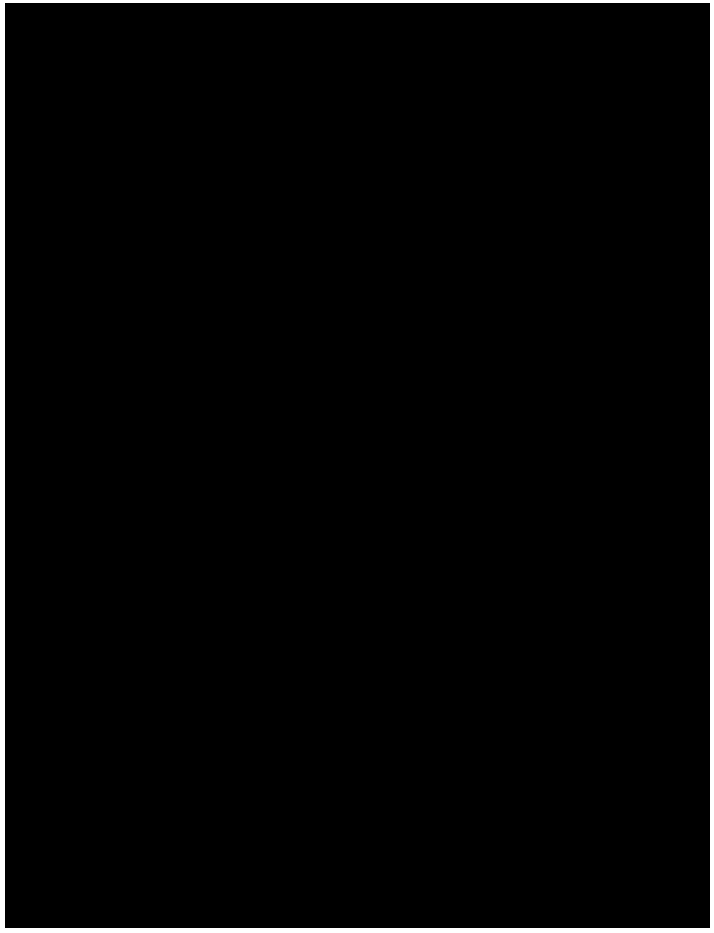


Figure 35: Treatment timeline by patient from baseline (placebo plus ADT), TITAN FA



Abbreviations: **Abbreviations**: AA, abiraterone acetate; APA, apalutamide; ENZA, enzalutamide; PD: Progressive disease; PFS2: Progression-free Survival on First Subsequent treatment; SubTX: Selected Subsequent therapy

Table 47. Number and % patients who crossed over, or switched to non-permitted treatments according to UK-rules and sample sizes (TITAN FA)

Treatment	Total	OS		PFS2	
		Switchers		Switchers	
		N	%	N	%
Apalutamide plus ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo plus ADT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADT: androgen-deprivation therapy; OS: overall survival; PFS2: progression-free survival on first subsequent treatment.

PFS2, TITAN FA

A different set of censoring rules were employed to implement the PFS2 KM analysis for the TITAN final analysis data cut to those used for the interim analysis. This was done to ensure that PFS2 events were more than OS events and hence preserve the modelling approach used in the original submission that partitions survival using rPFS, PFS2 and OS curves. Using the original censoring rules would result in implausible PFS2 KM curves that lie above the respective OS curves for each treatment arm. Definitions and results for the interim analysis and FA using trial censoring rules, and FA using alternative censoring rules are displayed in Table 48.

Table 48. Comparison of PFS2 across the data cuts; TITAN, ITT population

	TITAN interim analysis Trial censoring rules		TITAN FA Trial censoring rules		TITAN FA alternative censoring rules (used for this document)	
	Placebo plus ADT (n=527)	Apalutamide plus ADT (n=525)	Placebo plus ADT (n=527)	Apalutamide plus ADT (n=525)	Placebo plus ADT (n=527)	Apalutamide plus ADT (n=525)
Events, n (%)	121 (23.0)	87 (16.6)	[redacted]	[redacted]	[redacted]	[redacted]
Censored, n (%)	406 (77.0)	437 (83.2)	[redacted]	[redacted]	[redacted]	[redacted]
Median, month (95% CI)	NE (NE, NE)	NE (NE, NE)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	0.66 (0.50, 0.87)		[redacted]		[redacted]	
P value	0.0026		[redacted]		[redacted]	
PFS2 definition	PFS2, defined as the time from randomisation to investigator-assessed disease progression (PSA, radiographic, symptomatic, or any combination) during first subsequent anti-cancer therapy or death (any cause) prior to the start of the second subsequent anti-cancer therapy, whichever occurs first * Censoring date was either:		PFS2, defined as the time from randomisation to investigator-assessed disease progression (PSA, radiographic, symptomatic, or any combination) during first subsequent anti-cancer therapy or death (any cause) prior to the start of the second subsequent anti-cancer therapy, whichever occurs first * Censoring date was either:		PFS2, defined as the time from randomisation to investigator-assessed disease progression (PSA, radiographic, symptomatic, or any combination) during first subsequent anti-cancer therapy or death (any cause), whichever occurs first *Including deaths after first subsequent therapy	

	– Date Prior to Start of Second Subsequent Therapy – Date Last Known Alive	• Date Prior to Start of Second Subsequent Therapy • Date Last Known Alive	

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; FA, final analysis; HR, hazard ratio; ITT, intention-to-treat; NE, not estimable; PFS2, second progression-free survival

References

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Clinical expert statement & technical engagement response form

Apalutamide for treating prostate cancer [ID1534]

(this appraisal covers two indications metastatic hormone sensitive prostate cancer (mHSPC) and non-metastatic hormone relapsed prostate cancer (nmHRPC))

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

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In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **4 January 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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PART 1 – Treating a patient with this condition and current treatment options	
About you	
1. Your name	Professor Amit Bahl
2. Name of organisation	University Hospitals Bristol NHS Trust
3. Job title or position	Consultant Oncologist
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

nominating organisation's submission)	
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for this condition	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	This appraisal covers two indications: 1. For NMCRPC: The main aim of treatment is to delay metastases and improve survival without adversely affecting quality of life 2. For MHSPC: The main aim is to improve overall survival and maintain/improve quality of life.
9. What do you consider a clinically significant treatment	1. For NMCRPC: Delaying overt metastatic disease and improving survival 2. For MHSPC: Improving overall survival

response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	This is an area where there have been significant advances in management. The treatment options provide patients the opportunity of availing treatments with proven efficacy.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	For NMCRPC: There is option of using Darolutamide For MHSPC: There is option of using Docetaxel through NICE guidance. The CDF allows use of Enzalutamide.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE approvals for various treatments in the prostate cancer treatment pathway and CDF criteria for treatments.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	In England, the pathway of care is based on the NICE approvals and CDF criteria for treatments.

• What impact would the technology have on the current pathway of care?	1. In NMCRPC: Provide another option for treatment (Currently Darolutamide has NICE approval) 2. In MHSPC: Provide option of treatment with Apalutamide. Currently no NICE approved novel hormonal therapy in this setting. Only option is Docetaxel chemotherapy. The CDF allows use of Enzalutamide in the COVID pandemic.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Currently Apalutamide is not in use in routine NHS Clinical practice.
• How does healthcare resource use differ between the technology and current care?	Current care in NMCRPC has option of Darolutamide and the option of Apalutamide would be similar. In MHSPC, the current care is either ADT alone or ADT+Docetaxel based on NICE guidance and the option of ADT+Enzalutamide through CDF.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	In specialist cancer centres with Uro-oncology Multidisciplinary Team working.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The current treatment pathways should incorporate this technology with relative ease with no additional resource implications.
13. Do you expect the technology to provide clinically meaningful	Yes. Particularly in MHSPC where there is no NICE approved novel hormonal therapy option currently, this technology would provide a clinically meaningful benefit.

benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	In patients who otherwise would not have Docetaxel for MHSPC, this technology would increase length o life more than current care.
• Do you expect the technology to increase health-related quality of life more than current care?	By delaying onset on MCRPC state, it would be expected that the technology would increase health-related quality of life more than current care.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The trial data showed consistent benefit across the subgroups evaluated.
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	The technology would be easier to use than Docetaxel chemotherapy and similar as other novel hormonal therapies.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As with any treatment strategy, these patients are monitored regularly and as and when there is confirmation of disease progression or unacceptable toxicity, the treatment would be stopped.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	As is always the case, the collateral benefits of being able to save time from hospital appointments and being able to spend time with family/work/caring is not captured in the QALY benefits. By delaying requirement for more frequent treatment appointments and investigations, this technology would accrue more benefits.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	The novel hormonal therapies (including Apalutamide) make a significant and substantial impact on health related benefits and would be categorised as an innovation.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	The use of novel hormonal therapies is a 'step change' in the management of advanced prostate cancer with significant survival benefits.
• Does the use of the technology address any particular unmet need of the patient population?	The option for patients who would not wish to have chemotherapy or would have comorbidities precluding chemotherapye.g. pre-existing neuropathy.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Overall the side-effect profile is manageable and QOL data from trials supports that.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, the trails recruited patients from UK sites as well.
• If not, how could the results be extrapolated to the UK setting?	N/A

• What, in your view, are the most important outcomes, and were they measured in the trials?	Improvement in Overall Survival.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The AE's were captured adequately and at more frequent intervals than some comparative trials.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Real World data of Apalutamide in NMCRPC shows benefits similar to the trial data and side-effects similar.
Equality	

24a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
24b. Consider whether these issues are different from issues with current care and why.	N/A

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PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Selection of methods to adjust for treatment switching in the pivotal apalutamide clinical trials.	This is an area of statistical expertise. In NHS Clinical practice in England, the use of novel hormonal therapy will be guided by the guidelines and it will be used only once in the overall treatment pathway.
Clinical and cost effectiveness of apalutamide in people with mHSPC who are ineligible or	The issue of patients being unsuitable or ineligible for docetaxel chemotherapy has previously been considered by NICE in its evaluation of Radium 223 in MCRPC. Whilst several factors can be listed, however, it would not be feasible to get this as a subgroup from the TITAN trial.

unsuitable for docetaxel chemotherapy.	
Extrapolation of metastatic free survival / radiographic progression free survival	I would agree with the Weibull curve assumption.
Utility values for second and third line metastatic hormone relapsed prostate cancer (mHRPC) health states	I understand that the discrepancy between the ERG assumption and Company submission results in a minimal difference and as this question is beyond my area of expertise, I would not be able to comment further on this.
Market share of subsequent therapies used for metastatic hormone relapsed prostate cancer (mHRPC)	*The ERG notes that in the company's analysis a small proportion of patients with mHSPC treated with ADT alone received docetaxel as a subsequent treatment in the company. This is inappropriate for people ineligible/unsuitable for docetaxel in mHSPC, as by definition, they are not considered able to receive docetaxel.* The above statement does not recognise that some patients refuse docetaxel chemotherapy in MHSPC stage and are therefore unsuitable/ineligible for docetaxel in MHSPC, but they could accept docetaxel chemotherapy when the disease progresses to MCRPC state.

Duration of treatment costs for adverse events associated with docetaxel	The ERG assumption of calculating treatment costs for adverse events associated with docetaxel is short. There are some side-effects of Docetaxel e.g. neuropathy which can be long lasting. Therefore it would be better to use the 1 year duration for this assessment.
Are there any important issues that have been missed in ERG report?	No

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- In MHSPC, there is no NICE approved novel hormonal therapy option, and this technology offers a clinically meaningful benefit
- Side-effects from Docetaxel can take longer than 6 months to improve and may require longer term management
- Patient choice is a vital factor in treatment decision making and apart from medical reasons for Docetaxel ineligibility, the social factors and patient choicemake a significant contribution.
- This technology has significant improvements in overall survival in NMCRC and MHSPC
- Real World Evidence of Apalutamide shows similar results as trial data.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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Patient expert statement and technical engagement response form

Apalutamide for treating prostate cancer [ID1534]

(This appraisal will consider apalutamide in combination with androgen deprivation therapy for treating metastatic hormone sensitive prostate cancer and for treating non-metastatic hormone relapsed prostate cancer)

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form
In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

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In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **4 January 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

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PART 1 – Living with or caring for a patient with prostate cancer and current treatment options	
About you	
1.Your name	**Stephen Allen**
2. Are you (please tick all that apply):	■ a patient with prostate cancer? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with prostate cancer? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Tackle Prostate Cancer
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement

	■ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience. ■ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ■ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with prostate cancer If you are a carer (for someone with prostate cancer) please share your experience of caring for them.	I was diagnosed with prostate cancer 13 years ago and treated with an open radical prostatectemy. I have remained well and not required further treatment. I have been closely associated with the two major PCa Charities: Prostate Cancer UK and Tackle Prostate Cancer and through that have spoken with a large number of men who have experienced the many different forms of progressions of PCa and their associated treatments. I believe that I can adequately represent their views.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for prostate cancer on the NHS?	Already covered in the Organisation Submission I have already made on behalf of Tackle Prostate Cancer See responses to Q 7,8,9 of that submission.

That is, androgen deprivation therapy, or docetaxel in combination with androgen deprivation therapy for treating metastatic hormone sensitive prostate cancer Or Androgen deprivation therapy for treating non-metastatic hormone relapsed prostate cancer. 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	
8. If there are disadvantages for patients of **current NHS treatments** for prostate cancer (for example how the treatment is given or taken, side effects of treatment etc) please describe these	Already covered in the Organisation Submission I have already made on behalf of Tackle Prostate Cancer See response to Q 10 of that submission.
Advantages of this treatment	
9a. If there are advantages of apalutamide taken in combination with androgen deprivation therapy over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your	Already covered in the Organisation Submission I have already made on behalf of Tackle Prostate Cancer See response to Q 9 of that submission. The major advantages of this treatment are:

ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does apalutamide in combination with androgen deprivation therapy help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	• Reduction in severity of side effects compared with Docetaxel • Side effects of Docetaxel are more commonly seen in men with increased age and general 'frailty' • The drug is given orally and does not require specialised administration or hospital treatment
Disadvantages of this treatment	
10. If there are disadvantages of apalutamide taken in combination with androgen deprivation therapy over current treatments on the NHS please describe these? For example, are there any risks with apalutamide taken in combination with androgen deprivation therapy? If you are concerned about any	Already covered in the Organisation Submission I have already made on behalf of Tackle Prostate Cancer See response to Q 10 of that submission. There is the theoretical argument against Apalutamide (and, indeed, any drug treatment used at this stage) that this is a drug treatment that needs to be taken long-term – i.e. until it no longer controls the disease and progression occurs. Docetaxel is a treatment of a limited number of sessions. Taking long-term medication is no problem for patients – they are likely to be taking other such medication already. There is an argument that if such a drug is used very early in the treatment 'journey' the this restricts the choice of other treatments at a later stage when

potential side affects you have heard about, please describe them and explain why.	progression occurs – e.g. the use of Abiraterone or Enzalutamide. At a later stage Docetaxel may still be an option but not one that will often be tolerated by the patient. However, other options such as Radium223 or Lutetium may be appropriate for those patients. The majority of patients would opt for earlier and more effective treatment overall rather than 'save' such drugs for later in their treatment pathway.
Patient population	
11. Are there any groups of patients who might benefit more from apalutamide in combination with androgen deprivation therapy or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Already covered in the Organisation Submission I have already made on behalf of Tackle Prostate Cancer See response to Q 10, 11 of that submission. An important factor for some patients will be any difficulty in travelling to a hospital for treatment / supervision of therapy. Some patients will live a long distance away, some may have mobility issues, there may be poor availability of public transport for the patient etc. These essentially practical issues will certainly impact on the quality of life of many patients and may well influence their overall assessment of the treatment. Apalutamide will require regular monitoring with blood tests, but these can always be organised locally. Supervision and follow-up appointments can often be done remotely by telephone / video call – as has been shown by the recent Covid pandemic (with many patients reporting a preference for such appointments).
Equality	
12. Are there any potential equality issues that should be taken into account when considering prostate	NO

cancer and apalutamide in combination with androgen deprivation therapy? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	

Other issues	
13. Are there any other issues that you would like the committee to consider?	When this appraisal process was commenced, there was no approved treatment for non-metastatic hormone relapsed prostate cancer. Since then NICE have approved the use of Darolutamide in this specific stage of PCa. I know of no data that directly compares the efficacy of Apalutamide and Darolutamide.

PART 2 – Technical engagement questions for patient experts

Issues arising from technical engagement

We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.

Issues have been raised in the ERG report around 1) The appropriate statistical method to adjust clinical trial data for 1) people who	1) No relevant comments can be made by a patient. 2) This has already been discussed at other ongoing appraisals by Committee B. It would appear to be generally accepted that there are patients who can be deemed *'unsuitable'* for Docetaxel. There are no standard criteria that can always be used. Frailty scores my be part of that decision process but in general it should be the decisions of the individual clinician making unique decisions for each patient involved that is one of the most important factors

crossed over from the placebo arm of the trials to have apalutamide in combination with androgen deprivation therapy 2) people who went on to have follow on treatments that are not available in the NHS. (*Selection of methods to adjust for treatment switching in the pivotal apalutamide trials*) 2) Defining a potential group of people with metastatic hormone sensitive prostate cancer who would either be ineligible to have	Clinical effectiveness is of paramount importance – but no clinician would knowingly use a treatment that was not effective. Cost effectiveness is not an issue that patients can (or indeed should) pass an opinion on. We are not privy to the complex pricing / discounting processes that NHS England has with each pharma company. 3) No relevant comments can be made by a patient. 4) Men with hormone relapsed cancer will have a wide variety of symptoms depending on the stage of the disease. Commonly occurring symptoms are fatigue, weakness, pain, increasing urinary symptoms. Quality of life will considerably vary depending on the patient and the progression of disease. Treatments given earlier in the course of disease will increase the time to progression and onset of reduction in quality of life. I have no hard data concerning these statements but are opinion gained from talking with men with advanced prostate cancers. Perhaps it is also relevant to mention that increased quality of life experienced by the patient also has a considerable positive effect on those caring for the patient. The longer a patient can retain total independence of help from carers, then the better it is for both. 5) No relevant comments can be made by a patient. 6) Patients report a wide spectrum of symptoms during and after treatment with Docetaxel. I have never spoken with anyone who had no side effects at all. Problems are subjective – such as fatigue, nausea, weakness etc and objective such as bone marrow depression, increased incidence of concurrent infection, loss of hair and nails etc. Some patients require stays in hospital because of severe reduction in white cell count and serious infections. Some patients are given added medication to boost white cells – e.g. filgrastim. Some patients are regarded by their clinicians as needing such treatments as a prophylactic measure at the outset of treatment with Docetaxel. Side effects typically commence during treatment and may last for many weeks and even months in some patients. Severity and duration will depend on the general health of the patient, age and frailty. In general, the younger the patient the less likely they are to experience

docetaxel or for whom docetaxel would be unsuitable. Whether apalutamide in combination with androgen deprivation therapy is clinically and cost effective compared with androgen deprivation therapy alone in this group. (*Clinical and cost effectiveness of apalutamide in people with mHSPC who are ineligible or unsuitable for docetaxel chemotherapy*) 3) Whether the methods the company has used	severe and long-term side effects. It is not within the remit of a patient or support organisation to be able to comment on the *financial costs* of Docetaxel but certainly in terms of *personal costs* then the impact can be huge.

to extrapolate data beyond the trial period give plausible predictions of the proportions of people who have not progressed or who don't have metastases over the long term. (*extrapolation of survival curves: metastatic free survival (MFS) for nmHRPC, and radiographic progression free survival (rPFS) for mHSPC*) 4) Estimates of a person's quality of life whilst taking second and third	

treatments for prostate cancer once it has progressed to metastatic hormone relapsed prostate cancer. There was no trial quality of life data from SPARTAN or TITAN for people at this stage of the disease pathway. (*Utility values for second and third line metastatic hormone relapsed prostate cancer (mHRPC) health states*) 5) Estimates of the proportions of people who different treatment	

options for metastatic hormone relapsed prostate cancer and whether this is dependent on the treatments people had for metastatic hormone sensitive prostate cancer and non-metastatic hormone relapsed prostate cancer (*market share of subsequent therapies used in metastatic hormone relapsed prostate cancer*) 6) The types of side effects of treatment people may have with docetaxel,	

how long these side effects last and how long treatment for these side effects last. (*Duration of adverse event costs for docetaxel mHSPC*)	
15. Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- See bullet points given on Organisation Submission.
- There must now be one caveat – that statements that there is no currently available approved treatment for nmhrPCa are out of date. Darolutamide has now been approved by NICE in this context. Apalutamide may be an equally effective treatment to Darolutamide but direct comparative data may not exist. Where 2 drugs are equally effective clinically, then such factors as cost

may well become important. If both drugs are equally cost and clinically effective, then it would seem logical that both should be approved.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Apalutamide for treating prostate cancer [ID1534]

(This appraisal will consider apalutamide in combination with androgen deprivation therapy for treating metastatic hormone sensitive prostate cancer and for treating non-metastatic hormone relapsed prostate cancer)

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form
In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

NICE National Institute for Health and Care Excellence

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **4 January 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

NICE National Institute for Health and Care Excellence

PART 1 – Living with or caring for a patient with prostate cancer and current treatment options	
About you	
1.Your name	**Rebecca Leszczynski**
2. Are you (please tick all that apply):	☐ a patient with prostate cancer? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with prostate cancer? ☒ **a patient organisation employee or volunteer?** ☐ other (please specify):
3. Name of your nominating organisation.	Prostate Cancer UK
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement

	☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with prostate cancer If you are a carer (for someone with prostate cancer) please share your experience of caring for them.	For the purpose of this technical engagement response, we will focus on the use of apalutamide in the metastatic hormone sensitive prostate cancer setting. This is because firstly, we have data to demonstrate a sub-group within this population who are unsuitable for the comparator treatment, docetaxel chemotherapy, because of their older age and they therefore represent an unmet need. This sub-group currently only has access to androgen deprivation therapy (ADT) and, by using this standard of care as a comparator, there is potential for these patients to benefit from the additional months of life that apalutamide provides. Further, there is a group of men who have progressed from localised disease to metastatic hormone sensitive prostate cancer who similarly only have access to ADT. Men with advanced disease can present with a number of different symptoms. Evidenced symptoms for advanced prostate cancer can include[1]: • Fatigue, which can have a debilitating effect on everyday life and is linked with psychological distress.

	• Pain, most commonly caused by prostate cancer that has spread to the bones and which can have a significant impact on men's quality of life and mobility. • Urinary problems, this includes problems emptying the bladder, incontinence, blood in urine and kidney problems. This can have a debilitating effect on everyday life and is linked with psychological distress. • Bowel problems including constipation, diarrhoea, faecal urgency, faecal incontinence, pain, bowel obstruction and flatulence, which can cause physical and psychological distress and limit participation in daily and social activities. • Broken bones and repeated fractures caused by bone thinning that can impair mobility. • Sexual problems, including reduced libido and difficult getting or keeping an erection. This can lead to psychological distress, challenges with intimate relationships and can affect self-esteem • Lymphoedema, which manifests as swollen, sometimes disfigured extremities or truncal regions that can be uncomfortable, painful and cause functional impairment. • Anaemia, caused by damage to bone marrow. • Metastatic spinal cord compression, as cancer cells grow in or near the spine, which evidence suggests can occur in 1 to 12% of patients and requires urgent care and which, if not treated can lead to paralyses[2]. • Hypercalcaemia, caused by calcium leaking from the bones into the blood, which can result in symptoms such as nausea, vomiting and constipation. • Eating problems that can result in malnutrition Some or all of these symptoms can be life-changing and require a range of support services that research shows some men can struggle to access, either because of a lack of availability or because these services have a high demand. For example, The Life After Prostate Cancer Diagnosis Study (LAPCD) found that 56% of all men reported not being offered access to medications, devices, or specialist

	services to improve sexual function[3]. Further, access to exercise to reduce symptoms such as fatigue in men with advanced disease was found to be offered by only 17% of trusts surveyed[4].
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for prostate cancer on the NHS? That is, androgen deprivation therapy, or docetaxel in combination with androgen deprivation therapy for treating metastatic hormone sensitive prostate cancer Or Androgen deprivation therapy for treating non-metastatic hormone relapsed prostate cancer. 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	**<u>The metastatic hormone sensitive prostate cancer population</u>** The metastatic hormone sensitive prostate cancer population has two distinct populations. One is de novo, the other the result of disease progression from localised or locally advanced prostate cancer. There is level one evidence to demonstrate the effectiveness of docetaxel chemotherapy in the de novo metastatic population (STAMPEDE CHAARTED and GETUG-AFU). By contrast, there is limited evidence to support the use of chemotherapy in the population whose prostate cancer has progressed to metastatic disease. This is because the size of this population in all three trials was underpowered and cannot show statistical significance of treatment effect. In clinical practice, the standard of care is docetaxel chemotherapy for men with newly diagnosed hormone-sensitive metastatic prostate cancer (mHSPC), unless they are unsuitable for it. During the COVID-19 pandemic, enzalutamide has been made available to these patients. Abiraterone is available to those patients that cannot tolerate enzalutamide. Without this interim provision of Novel Hormone Agents (NHAs) hormone-sensitive metastatic prostate cancer patients who are unsuitable for docetaxel chemotherapy would receive ADT. We also understand from several clinicians that docetaxel chemotherapy – or during the COVID-19 pandemic, enzalutamide or abiraterone – is made available to men whose cancer has progressed to become metastatic. We will focus below on those patients who are only able to access ADT – those who are unsuitable, those who have progressed from localised/locally advanced

	disease and those who have progressed from newly diagnosed metastatic prostate cancer but are still castration sensitive. 1. **<u>Newly Diagnosed Hormone Sensitive Prostate Cancer who are unable to have chemotherapy</u>** In 2016, docetaxel chemotherapy with ADT became the standard of care for patients newly diagnosed with metastatic hormone sensitive prostate cancer (mHSPC). For a previous appraisal of abiraterone in newly-diagnosed mHSPC, Prostate Cancer UK shared data from Public Health England that shows that a significant proportion of men newly diagnosed at this stage of the disease did not receive chemotherapy. Specifically, 63.6% of men with a new diagnosis of mHSPC aged under 70 receive chemotherapy but this starkly decreases to 21.9% for men aged over 70 and drops further to 5.7% for men aged 80 and above.[5] Most of these men are likely only receiving ADT and have no other life extending treatments available to them, and are missing out on the 14 extra months of life that docetaxel can provide (57.6 months vs. 44.0 months; hazard ratio 0.61; 95% confidence interval [CI], 0.47 to 0.80; P<0.001).[6] Likely, this lack of access to docetaxel is an informed decision based on the harsh side effect profile of docetaxel, which these older men are more likely to be unable to tolerate. Side effects with docetaxel are reported mostly during treatment and in the first 6 months after treatment. Tannock et al reported that 53% of patients experienced fatigue, 65% of patients experienced alopecia, 42% experienced nausea/vomiting, 32% experienced diarrhoea and 30% experienced nail changes with docetaxel every 3 weeks.[7] Docetaxel treatment means repeatedly going into hospital, often to clinic on one day followed by chemotherapy the next day approximately every three weeks for 6 cycles of treatment. Patients are also required to self-monitor between visits, to be vigilant, recognise and to present back to hospital should any adverse reactions to treatment occur, for example,

should they become febrile. There is potential for this treatment regime to be physically challenging and potentially not suitable for older men.

However, having ADT alone means these older men lose out on the potential for additional months of life that patients able to tolerate chemotherapy gain. They are also often living with the progressive symptoms of the disease that can limit their quality of life.

THE TITAN trial shows that there is benefit in terms of progression free survival (PFS) in some older men aged 65-74 of whom some will not receive chemotherapy, as we see a sharp decrease in chemotherapy uptake in men above 70. The hazard ratio (HR) for PFS is 0.47(CI 0.34–0.64) in favour of apalutamide in en aged 65-74. A delay to progression can give older men a longer period with a better quality of life than if they only receive ADT, as it can enable to delay the often challenging impacts of hormone-refractory prostate cancer. However, this does not translate to an overall survival (OS) benefit as in the under 65 age group the HR is 0.56 (0.33–0.94), but this decreases to 0.73 (0.48–1.10) and 0.74 (0.41–1.35) in the 65-75 and 75+ age groups respectively.[8]

2. **<u>Men who have progressed from localised or locally advanced prostate cancer to hormone sensitive metastic prostate cancer</u>**

Evidence based guidance only recommends men with newly diagnosed mHSPC cancer receive docetaxel and does not extend to those who have progressed from localised/locally advanced disease. We are aware that some clinicians offer men who have progressed docetaxel, but there is no clear guidance. The key trials evidencing use of docetaxel, GETUG-AFU, CHAARTED and STAMPEDE were mainly made up of men with newly-diagnosed metastatic prostate cancer. In GETUG-AFU, 71% were metastatic at diagnoses, in CHAARTED, 73% had no previous curative therapy and in STAMPEDE 94% were newly diagnosed (62% metastatic), with 6% with recurrent disease and 48% metastatic. This limited the

	sub-group analyses of the progressed to metastatic prostate cancer population, as the small size of the population was too underpowered to demonstrate benefit. Given this, NICE Guidelines and NHS England Commissioning Policy only recommend for the use of docetaxel in the newly diagnosed metastatic population. Further long-term analysis from the CHAARTED trial could not demonstrate statistically significant benefit from docetaxel for those who had prior local therapy (HR 0.97, 95% CI 0.58–1.56).[6] Based on this evidence, there is significant unmet need in these patients. However, the HR for OS was 0.40 (0.15–1.03) in favour of apalutamide in the TITAN trial. By contrast, the HR for PFS was 0.41 (0.22–0.78) suggesting there may be a PFS benefit in this population who currently lack treatment options, but an understanding of the effect that their receiving apalutamide would have on their subsequent treatments is needed.[8] **3. <u>Men who are metastatic hormone sensitive who have progressed</u>** Currently, these men would similarly only be eligible for ADT or docetaxel rechallenge if they were suitable for chemotherapy based on evidence-based NICE guidance. Therefore, is it clear that there are several sub-populations within the mHSPC population that will only be having ADT and thus have no extending treatment options available to them. **<u>The non-metastatic castrate resistant population</u>** Men with non-metastatic castrate resistant prostate cancer currently have Darolutamide as a treatment option and therefore the un-met need in this population is not as significant.

8. If there are disadvantages for patients of **current NHS treatments** for prostate cancer (for example how the treatment is given or taken, side effects of treatment etc) please describe these	Docetaxel is a treatment with significant side effects. Tannock et al reported that 53% of patients experienced fatigue, 65% of patients experienced alopecia, 42% experienced nausea/vomiting, 32% experienced diarrhoea and 30% experienced nail changes with docetaxel every 3 weeks.[7] Docetaxel treatment means repeatedly going into hospital, often to clinic on one day followed by chemotherapy the next day approximately every three weeks for 6 cycles of treatment. Patients are also required to self-monitor between visits, to be vigilant, recognise and to present back to hospital should any adverse reactions to treatment occur, for example, should they become febrile. There is potential for this treatment regime to be physically challenging and potentially not suitable for older men. For those men unable to have docetaxel, men on ADT miss out on additional months of life and have a shorter life expectancy. Likely, these men are unable to have docetaxel through no fault of their own, and it might be as a result of their age or frailty status.
Advantages of this treatment	
9a. If there are advantages of apalutamide taken in combination with androgen deprivation therapy over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others?	Treatment with apalutamide reduces the risk of death in patients with mHSPC, compared with ADT. In the TITAN trial, the overall survival percentage at 24 months was 82.4% in the apalutamide group and 73.5% in the placebo (ADT) group (hazard ratio for death, 0.67; 95% CI, 0.51 to 0.89; P = 0.005), resulting in a 33% lower risk of death. This is a distinct advantage for men that only receive ADT – which equated to 66% of the mHSPC population in 2016.[5] Treatment with apalutamide also reduces the risk of radiographic progression in men with mHSPC. In the TITAN trial, patients had a 52% lower risk of radiographic progression or death at 24 months compared. A consistent benefit was seen across all sub-groups, including patients in all age categories, disease volume, Gleason score and ECOG status.[8]

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does apalutamide in combination with androgen deprivation therapy help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	Patients are also able to maintain a good quality of life while being treated with apalutamide. In the TITAN trial, analysis of change from baseline in the functional assessment of cancer therapy - Prostate (FACT-P) score showed that health related quality of life was maintained with apalutamide. This quality of life is particularly important compared to the quality of life deficit that patient's experience with docetaxel, with some patients not being able to tolerate this at all, and therefore have no other treatment options. Although no head-to-head comparisons of quality of life with docetaxel and apalutamide have taken place, there is evidence showing a comparison in quality of life between abiraterone and docetaxel.[9] As abiraterone is a NHA, this evidence could be of value to the appraisal.
Disadvantages of this treatment	
10. If there are disadvantages of apalutamide taken in combination with androgen deprivation therapy over current treatments on the NHS please describe these? For example, are there any risks with apalutamide taken in combination with androgen deprivation therapy? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	In the TITAN trial, the frequency of grade 3 or grade 4 events was 42.2% in the apalutamide group and 40.8% in the placebo group. Notably, rash of any grade is the most common side effect associated with apalutamide, incidence was 27.1 in the apalutamide group vs 8.5% in the placebo group. [8]

Patient population	
11. Are there any groups of patients who might benefit more from apalutamide in combination with androgen deprivation therapy or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	In the mHSPC indication, patients who are unsuitable for docetaxel may benefit from having access to apalutamide, otherwise they have no other life extending treatments available to them. In the TITAN trial, men who were less than 65 had a HR for PFS of 0.45 (0.31- 0.66) in favour of apalutamide. This benefit was maintained in men aged 65-74, with a HR for PFS of 0.47 (0.34–0.64). In this older age group above 70 we see the uptake of docetaxel decrease substantially. They therefore can benefit from the additional months of life with a better quality of life before progressing. The OS, although favourable towards apalutamide, does not show a statistically significant benefit in older men. In the under 65 age group the HR is 0.56 (0.33–0.94), but this decreases to 0.73 (0.48–1.10) and 0.74 (0.41–1.35) in the 65-75 and 75+ age groups respectively. Further, and as previously detailed, there is no evidence-based guidance to support the use of docetaxel in men who have progressed from localised/locally advanced disease. There is variation in clinical practice for these patients as a result of this. The sub-group in the TITAN trial who had progressed from localised or locally advanced disease was underpowered to determine benefit. The HR for overall was 0.40 (0.15–1.03) in favour of apalutamide and the HR for PFS was 0.41 (0.22–0.78). This shows there is a benefit in terms of cancer progression for this population and suggested benefit in terms of OS.

Equality	
12. Are there any potential equality issues that should be taken into account when considering prostate cancer and apalutamide in combination with androgen deprivation therapy? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-	As previously detailed, older patients are less likely to receive docetaxel, likely due to being unable to tolerate the side effects and therefore a large proportion of men do not have the option of the months of additional life. We consider that is unlikely to be due to patient choice, as we would not expect to see such a stark decrease with increasing age. Further, this effect parallels that of the uptake by older men of radical prostatectomy, where Prostate Cancer UK's analysis of other data in the Public Health England dataset shows a drop from 27% to 3% in the same age range. Therefore, it is unlikely that in both cases the sharp decrease in uptake by age is explained purely by patient choice, but by clinical decision over the physical burden on the patient from the treatment in question. Not making this treatment available means that older patients are unable to experience the benefit from the additional months of life of any treatment, and have no treatment options available to them, except ADT alone. This is therefore a potential equality issue and should be taken into account when considering apalutamide in men with mHSPC.

real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Issues have been raised in the ERG report around 1) The appropriate statistical method to	Issue 2: Prostate Cancer UK has provided evidence to another appraisal for abiraterone in men with newly diagnosed mHSPC to show that there is a cohort of patients who are unable to have docetaxel. Specifically, older patients are less likely to receive docetaxel, likely due to being unable to tolerate the side effects and therefore a large proportion of men do not have the option of the months of additional life.

adjust clinical trial data for 1) people who crossed over from the placebo arm of the trials to have apalutamide in combination with androgen deprivation therapy 2) people who went on to have follow on treatments that are not available in the NHS. (*Selection of methods to adjust for treatment switching in the pivotal apalutamide trials*) 2) Defining a potential group of people with metastatic hormone sensitive prostate	We consider that is unlikely to be due to patient choice, as we would not expect to see such a stark decrease with increasing age. Further, this effect parallels that of the uptake by older men of radical prostatectomy, where Prostate Cancer UK's analysis of other data in the Public Health England dataset shows a drop from 27% to 3% in the same age range. Therefore, it is unlikely that in both cases the sharp decrease in uptake by age is explained purely by patient choice, but by clinical decision over the physical burden on the patient from the treatment in question. We know that this is just one factor that affects an individual's ability to tolerate docetaxel and that patients who are unsuitable for chemotherapy can be identified by clinicians using their clinical judgement and through clear communication and understanding patients can make an informed decision. **Issue 5 - Subsequent therapies:** There is insufficient evidence to determine who might have clinical benefit from having novel hormone agents similar to apalutamide after progressing on apalutamide. **Issue 6 – duration of adverse events cost for Docetaxel in mHSPC** Data presented at ASCO in February 2020 showed quality of life data for abiraterone compared to on Docetaxel. Over the two years that global QoL was measured, there was a decrease in QoL for docetaxel. This evidence can be used in the modelling to consider the benefit of the treatment and the length of the benefit of docetaxel.[9]

cancer who would either be ineligible to have docetaxel or for whom docetaxel would be unsuitable. Whether apalutamide in combination with androgen deprivation therapy is clinically and cost effective compared with androgen deprivation therapy alone in this group. (*Clinical and cost effectiveness of apalutamide in people with mHSPC who are ineligible or unsuitable for docetaxel chemotherapy*)	

3) Whether the methods the company has used to extrapolate data beyond the trial period give plausible predictions of the proportions of people who have not progressed or who don't have metastases over the long term. (*extrapolation of survival curves: metastatic free survival (MFS) for nmHRPC, and radiographic progression free survival (rPFS) for mHSPC*)	

4) Estimates of a person's quality of life whilst taking second and third treatments for prostate cancer once it has progressed to metastatic hormone relapsed prostate cancer. There was no trial quality of life data from SPARTAN or TITAN for people at this stage of the disease pathway. (*Utility values for second and third line metastatic hormone relapsed prostate cancer (mHRPC) health states*)	

5) Estimates of the proportions of people who different treatment options for metastatic hormone relapsed prostate cancer and whether this is dependent on the treatments people had for metastatic hormone sensitive prostate cancer and non-metastatic hormone relapsed prostate cancer (*market share of subsequent therapies used in metastatic hormone relapsed prostate cancer*)	

6) The types of side effects of treatment people may have with docetaxel, how long these side effects last and how long treatment for these side effects last. (*Duration of adverse event costs for docetaxel mHSPC*)	
15. Are there any important issues that have been missed in ERG report?	
PART 3 -Key messages	
16. In up to 5 sentences, please summarise the key messages of your statement: • Apalutamide could benefit older patients who are less likely to be able to have docetaxel and therefore can only access ADT, resulting in a shorter life expectancy. Apalutamide could delay prostate cancer progression and provide these patients with a better	

quality of life for longer than if they only received ADT. This benefit needs to be compared to the benefit they would receive from subsequent treatments, especially if it will prevent access to other NHAs.

- Apalutamide could benefit those patients who have progressed from localised disease and for whom there are no evidence based treatment options except ADT. There is a demonstrated benefit in terms of PFS and a suggested benefit for OS but an analysis across the whole pathway is necessary to understand if the PFS benefit is lost due to restrictions in potential future treatments. A better understanding of the use of apalutamide on patients' treatment sequence is needed.
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

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References:

(1) References for each symptom available on request.
(2) Tazi, H. et al (2003). *Spinal Cord Compression in Metastatic Prostate Cancer. European Urology, 44(5), 527–532.*
(3) Downing A, et al (2019) Quality of life in men living with advanced and localised prostate cancer in the UK: a population-based study. Lancet Oncol 20: 436-47
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(5) *Get Data Out*, Public Health England. Available at https://www.cancerdata.nhs.uk/getdataout/data [Accessed 08/01/20]
(6) Sweeney, C. J.et al . (2015).*Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. New England Journal of Medicine, 373(8), 737–746.* doi:10.1056/nejmoa1503747
(7) Tannock, I. F. et al. (2004). *Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer. New England Journal of Medicine, 351(15), 1502–1512.*
(8) Chi, K et al (2019) Apaltuamide for Metastatic, Castration-Sensitive Prostate Cancer, N Engl J Med 381:13-24
(9) Rush, HL (2020) 'Comparative quality of life in patients randomized contemporaneously to docetaxel or abiraterone' [Poster presented at ASCO, February 2020]

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Technical engagement response form

Apalutamide for treating prostate cancer [ID1534]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments: **11 January 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

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- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, 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 engagement 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.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Bayer plc**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: selection of methods to adjust for treatment switching in the pivotal apalutamide clinical trials (nmHRPC and mHSPC)	**NO**	Please provide your response to this key issue, including any new evidence, data or analyses As various adjustment methods are informed by different assumptions, none of which seem to be fully aligned with the SPARTAN and TITAN data, all available methods should be considered in decision making as well as the range of potential relative efficacy and cost-effectiveness estimates they produce. Only adjusting for one novel therapy per patient may not be sufficient to align the subsequent treatments in the trial data with the subsequent treatments in clinical practice, given that patients in clinical practice would also receive relatively more treatment with other agents such as docetaxel, radium-223, or cabazitaxel following apalutamide + ADT compared to ADT alone. Hence, differences in these other subsequent treatments between the trials and current/proposed clinical practice are also a potential confounding factor of the relative treatment benefit that should be adjusted for and accounted in decision making.
Key issue 2: clinical and cost effectiveness of apalutamide in people with mHSPC who are	**NO**	Please provide your response to this key issue, including any new evidence, data or analyses The comparison of apalutamide + ADT against ADT in patients ineligible for chemo is based on the TITAN population. However, it is not clear whether the

eligible or unsuitable for docetaxel chemotherapy		TITAN population is fully reflective of a chemo ineligible population which may have different clinical characteristics and prognosis that may result in different relative efficacy and cost-effectiveness estimates compared to the ones based on the TITAN population. A post-hoc analysis of the TITAN population in which chemo-ineligibility is carefully defined and identified should be considered in decision making.
Key issue 3: extrapolation of survival curves: metastatic free survival (MFS) for nmHRPC and radiographic progression free survival (rPFS) for mHSPC	**NO**	Please provide your response to this key issue, including any new evidence, data or analyses It is not clear in the company submission which data-cut informs the time on treatment (ToT) analysis and how the ToT data compares with the MFS and rPFS data given that apalutamide should be administered until progression as per the SmPC. The data-cut for ToT should coincide with the data-cuts for the MFS and rPFS analyses (i.e. first data-cut), otherwise any data-cut later than that would likely contain relatively more discontinuation events causing the extrapolated ToT curve to diverge further from the MFS and rPFS treatment curves, potentially underestimating treatment costs relative to the disease progression benefit. OS treatment effect waning: In current UK practice patients have access to more life-extending treatment options (i.e. novel therapies such as enzalutamide and abiraterone) once they progress to mHRPC. In the new proposed treatment pathway, patients would not have access to these novel agents once they progress to mHRPC following prior treatment with apalutamide because the commissioning policy rule around reimbursing a single novel hormonal agent in the prostate cancer treatment pathway. Therefore, the survival of patients in the mHRPC state can be expected to be lower in the new proposed pathway due to the reduced number of life-extending treatment options patients have access to. In the company model, the aggregated survival of patients in the mHRPC state following apalutamide + ADT treatment for mHSPC exceeds that of patients following ADT alone. In order to accurately reflect clinical practice, a treatment waning of the OS benefit and

		potential reversal would have to be implemented on progression to mHRPC in the model. It is not clear in the company submission whether any subsequent treatments were allowed in SPARTAN and TITAN prior to progression, but the MFS and rPFS curves should also be adjusted to remove the confounding of therapies not permitted for nmHRPC and mHSPC in the UK.
Key issue 4: utility values for second and third line metastatic hormone relapsed prostate cancer (mHRPC) health states	**NO**	Please provide your response to this key issue, including any new evidence, data or analyses Utility values in the mHRPC states should be linked to the subsequent therapies received. For instance, following treatment with apalutamide + ADT patients would mainly receive docetaxel as first line subsequent treatment for mHRPC in contrast to novel agents (enzalutamide/abiraterone) following ADT alone, which is expected to negatively impact their utility. Hence, differential utilities should be applied in the mHRPC state linked to the subsequent treatments received in each arm – applying the same utilities can potentially bias the cost-effectiveness estimates in favour of apalutamide. Utility values should be consistent in the mHRPC health states following progression from both nmHRPC and mHSPC. Utilising consistent utilities from previous appraisals for the 1st mHRPC state should be explored rather than deriving this based on SPARTAN and TITAN separately, which yields inconsistent values.
Key issue 5: market share of subsequent therapies used in metastatic hormone relapsed prostate cancer (mHRPC)	**NO**	Please provide your response to this key issue, including any new evidence, data or analyses The cost of subsequent treatments seems to be applied for the entire duration a patient spends in each mHRPC state in the model, as opposed to being based on the time on treatment specific to each treatment at that point in the pathway (which can be sourced from their respective clinical trials). This can overestimate the true cost

		of subsequent therapy especially for costly novel therapies like enzalutamide and abiraterone. There seems to be a mismatch between the time spent in each subsequent mHRPC state and the actual treatment received. For instance, the duration of BSC from TA387 in the first mHRPC state is applied following treatment with apalutamide + ADT, whereas in clinical practice these patients will likely receive docetaxel sooner, in first line mHRPC, rather than BSC.
Key issue 6: Duration of adverse event costs for docetaxel (mHSPC)	**NO**	Please provide your response to this key issue, including any new evidence, data or analyses Administration costs: Cost of pharmacist dispensing time for oral therapies should be applied in the model. HRU: There is a high discrepancy in frequency of monitoring in the mHSPC state between treatment with apalutamide+ADT/ADT alone and treatment with docetaxel + ADT.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Additional issue 1: Relevant comparator in the nmHRPC population	p. 31	**YES**	Darolutamide, another second-generation androgen receptor inhibitor (ARI) such as apalutamide, has been recommended by NICE to be used alongside ADT in adult patients with high-risk nmHRPC (TA660, published 25 November 2020). Therefore, darolutamide + ADT is the current relevant comparator for apalutamide + ADT in the nmHRPC population. However, the only comparator considered in the current appraisal in the nmHRPC population was ADT alone, which is being replaced by the superior effectiveness and cost-effectiveness of darolutamide + ADT in clinical practice. Therefore, ADT is no longer the relevant comparator in this population. The reasons as to why darolutamide has not been included in the scope of this appraisal (subject to its ongoing appraisal) are not clear, since enzalutamide and abiraterone have been included in the scope for the mHSPC population. This should be considered a key issue.
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	**Company's base case before technical engagement**	**Change(s) made in response to technical engagement**	**Impact on the company's base-case ICER**
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

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

Apalutamide for treating prostate cancer

Evidence Review Group's summary and critique of the company's response to technical engagement

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
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Date completed	19th January 2021

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LIST OF ABBREVIATIONS

1L	First line
2L	Second line
3L	Third line
ADT	Androgen deprivation therapy
AE	Adverse event
AIC	Academic in confidence
APA	Apalutamide plus ADT
CI	Confidence interval
CIC	Commercial in confidence
CS	Company submission
CSR	Clinical study report
DOX	Docetaxel plus ADT
DSU	Decision Support Unit
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
EQ-VAS	EuroQol Visual Analogue Scale
ERG	Evidence Review Group
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
Incr	Incremental
IPCW	Inverse probability of censored weights
IPD	Individual patient level data
IPE	Iterative parameter estimation
ITT	Intent to treat
KM	Kaplan Meier
LY	Life-years
LYG	Life-years gain
mCSPC	Metastatic castration sensitive prostate cancer
MFS	Metastasis-free survival
mHRPC	Metastatic hormone relapsed prostate cancer
mHSPC	Metastatic hormone sensitive prostate cancer
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
nmCRPC	Non metastatic castration relapsed prostate cancer
nmHRPC	Non metastatic hormone relapsed prostate cancer
NR	Not reported
OS	Overall survival
PAS	Patient Access Scheme
PSA	Prostate specific antigen
PFS	Progression free survival
PFS2	Secondary progression free survival
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
rPFS	Radiographic progression free survival
RPFSTM	Rank Preserving Structural Failure Time Model
RR	Relative risk/risk ratio
SAE	Serious adverse event

SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
SPARTAN	Selective Prostate AR Targeting with ARN-509
STA	Single Technology Appraisal
TA	Technology appraisal
TE	Technical engagement
TEAE	Treatment-emergent adverse event
TITAN	Targeted Investigational Treatment Analysis of Novel Anti-androgen
TSD	Technical Support Document
TTD	Time to treatment discontinuation

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 key issues for technical engagement (TE) proposed in the ERG report for this appraisal (submitted to NICE on 8th October 2020). The ERG received the company's response on 5th January 2021.

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

- A written response to each of the six key issues, three of which include new evidence and/or analyses (see Table 1).
- Updated clinical effectiveness results (including overall survival (OS) and safety outcomes) from the final data cut of the pivotal phase III TITAN trial of apalutamide for the treatment of metastatic hormone sensitive prostate cancer (mHSPC).
- An updated network meta-analysis (NMA) for the indirect comparison of apalutamide plus ADT versus docetaxel plus ADT, incorporating the final results from the TITAN trial (OS and safety outcomes).
- A set of updated cost-effectiveness results for both the 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).
    - Additional evidence and/or analyses provided by the company in response to some of the key issues for TE.
    - Updated clinical effectiveness estimates of apalutamide in the mHSPC indication informed by the final TITAN data cut (OS and safety outcomes) and, in turn, the updated NMA.
- An updated version of the company's economic model accompanies the response form.

In this report we present the following:

- Our critique of the company's response to each of the six issues for technical engagement (Section 2)
- A validation of the results of the company's updated cost-effectiveness analysis, and the results of an updated ERG base case and scenario analyses (Section 3)
- A summary and critique of the final results of the TITAN trial (Appendix 4.1)
- A summary and critique of the updated NMA (Appendix 4.2).

Table 1 Summary of key issues for technical engagement

Issue number	Summary of issue	Does this response contain new evidence, data or analyses?
1	Selection of methods to adjust for treatment switching in the pivotal apalutamide clinical trials	Yes – additional evidence and updated cost effectiveness analysis
2	Clinical and cost effectiveness of apalutamide in people with mHSPC who are ineligible or unsuitable for docetaxel chemotherapy	Yes – additional evidence (from other NICE appraisals)
3	Extrapolation of metastatic free survival / radiographic progression free survival	No
4	Utility values for second- and third-line metastatic hormone relapsed prostate cancer (mHRPC) health states	No
5	Market share of subsequent therapies used in metastatic hormone relapsed prostate cancer (mHRPC)	No
6	Duration of treatment costs for adverse events associated with docetaxel	Yes – additional evidence (real world data)

2. Critique of the company's response to key issues for technical engagement

2.1 Issue 1 – Selection of methods to adjust for treatment switching in the pivotal apalutamide clinical trials (nmHRPC and mHSPC)

As noted in the ERG report, there is uncertainty about the company's selection of the method to adjust survival outcomes to account for the effect of patients switching between treatments in the phase III pivotal clinical trials (SPARTAN in nmHRPC and TITAN in mHSPC)**.** In both trials, patients crossed over from placebo to apalutamide when the trials were unblinded at interim analyses. Also, for the purposes of this appraisal, the subsequent treatments received by patients in the trials were adjusted in the cost effectiveness analysis to comply with NHS England commissioning policy restricting the use of novel agents (apalutamide, abiraterone and enzalutamide) to one per patient. The company selected a

(currently unpublished) ‘modified’ version of the Rank Preserving Structure Failure Time Model (RPSFTM) adjustment method using data from an external clinical trial, COU-AA-302 (an RCT comparing abiraterone acetate plus prednisone versus prednisone in metastatic castrate resistant prostate). Other available adjustment models (e.g. the iterative parameter estimation (IPE), the two-stage method), as published in the NICE DSU TSD 16, were considered for use, but were not selected due to insufficient trial data, and because some of the cost-effectiveness results were considered by the company to be counter intuitive and clinically implausible. The company therefore did not report cost effectiveness analyses according these adjustment methods in their submission.

The ERG requested that the company provide (as illustrative scenario analyses) the cost effectiveness results based on all adjustment methods considered, at technical engagement. The purpose would be to illustrate the sensitivity of the ICERs according to different assumptions about treatment switching, and thus facilitate a fully-informed appraisal committee consideration of the available evidence. In their response to technical engagement the company reiterate their selection judgements but, with the exception of the inverse probability of censored weights (IPCW) method for the TITAN trial, they do not provide the cost-effectiveness results for each of the respective methods, as was requested.

Rather, the company elected to address other uncertainties associated with the process of adjusting the survival estimates, one of which was discussed in the ERG report (section 4.2.6.2), though it was not explicitly cited as a key issue for technical engagement. To recap, the ERG was unclear from the company submission (CS) whether the survival estimates from the COU-AA-302 trial itself had been adjusted for crossover when estimating the shrinkage factors for subsequent novel therapy adjustment in the SPARTAN and TITAN trials. If the COU-AA-302 estimates used in the ‘modified’ RPFSTM had not been adjusted for crossover, the clinical effectiveness of apalutamide was likely to be overestimated.

In their response to technical engagement, the company considers evidence from two data cuts in COU-AA-302: interim analysis 3 (IA3) and final analysis (FA). Data from the latter data cut was used in the company’s analysis reported in the CS.

The company acknowledge that the survival estimates from the FA cut-off may be affected by crossover because 93 patients (which represent 17% of the 542 patients originally randomised to the prednisone alone arm) had switched to the active treatment by the FA data cut-off. However, they suggest that the impact should be minimal for the IA3 data cut as only three patients (0.55%) had crossed over at that stage.

In order to demonstrate that the impact of adjustment for crossover in COU-AA-302 on the economic outcomes is negligible, the company compared the OS hazard ratios (HRs) for apalutamide plus ADT versus placebo plus ADT in SPARTAN and TITAN estimated from the IA3 and FA data cuts *without making any adjustment for the cross-over in COU-AA-302 (our emphasis).*

2.1.1 'Modified' RPSFTM adjustment for SPARTAN and TITAN based on COU-AA-302 trial data

2.1.1.1 SPARTAN: nmHRPC

The results for the adjustment of OS in SPARTAN informed by external data from COU-AA-302 are shown in TE response Table 3 (utilising FA data) and Table 4 (utilising IA3 data) for analyses with and without re-censoring respectively. The latter approach (IA3 data without re-censoring) was selected for the company's base case.

In the analysis without re-censoring, the OS HRs derived from IA3 and FA data were quite similar: [redacted] and [redacted] (see TE response Table 3 and Table 4, and the resulting Kaplan-Meier OS plots for apalutamide plus ADT and ADT alone in TE response in Figures 13 and 14).

The company, therefore, argues that the adjustment of survival estimates from COU-AA-302 for crossover would have only a limited impact on the results of the economic analysis. We note that in the analyses with re-censoring, the OS HR for the FA cut-off is only slightly higher than that for IA3 ([redacted] versus [redacted]).

The company states that the secondary progression-free survival (PFS2) estimates were not available at the IA3 cut-off in COU-AA-302 and, therefore, a comparative analysis for IA3 and FA cut-offs could not be conducted.

ERG conclusions

- Based on the estimates provided by the company, the choice of interim or final data cut of in the COU-AA-302 trial appears to have only a limited impact on the adjusted OS HRs in SPARTAN used in the company's base case.
- Importantly, 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). Therefore, it

is likely that the crossover adjustment of PFS2 estimates from COU-AA-302, if conducted, would have had a more pronounced effect on the adjusted HRs in SPARTAN and TITAN, and increased the ICERs.

- We would like to emphasise that the estimates presented by the company could not be verified by the ERG due to the lack of access to individual patient data.

2.1.1.2 TITAN: mHSPC

The HRs for the adjustment of OS in TITAN are shown in TE response Table 6 (utilising FA data) and Table 7 (utilising IA3 data) for analyses with and without re-censoring. The estimates for both data cuts seem to be very similar.

Adjusted HRs for PFS2 in TITAN, derived using the FA data cut from COU-AA-302, are shown in TE response Table 8. We note that they are quite similar to those reported in CS Appendix R.2.3 Table 9 for the first data cut in TITAN. It is not clear, however, whether these estimates are comparable because, as the company states, they were derived using different censoring rules.

According to the TE response, a different set of censoring rules was employed by the company to implement the PFS2 Kaplan-Meier analysis for the TITAN final data cut to those used for the interim analysis. The original rules censored patients at the last known date alive, or at the date prior to start of second subsequent therapy. Under the alternative censoring rules patients were not censored at the start of a second subsequent therapy (page 119 and Table 48 of TE Response). The company states that this was done to ensure that "*PFS2 events were more than OS events and hence preserve the modelling approach used in the original submission that partitions survival using rPFS, PFS2 and OS curves. Using the original censoring rules would result in implausible PFS2 KM curves that lie above the respective OS curves for each treatment arm"* (further details are provided in TE response pages 119-121).

The ERG notes that the HRs estimated by the respective sets of censoring rules are broadly similar, but that the alternative censoring rules generated the lower of the two HRs and has narrower confidence intervals. Thus, the choice of alternative censoring rules for the base case, albeit for modelling purposes, gives a slightly more favourable estimate of the clinical effectiveness of apalutamide plus ADT (see Appendix 4, section 4.1.2 of this document for further detail).

In TE response Tables 33 and 34, the company reports goodness of fit statistical values (AIC and BIC) for the six parametric distributions used for extrapolation of PFS2 and OS in the final base-case analysis for TITAN (Weibull, exponential, Gompertz, log-normal, log-logistic and generalised gamma). We note that the Weibull fits, selected for the company's base case, had intermediate AIC and BIC scores.

ERG conclusions

- In the base-case analysis for the mHSPC indication, the company uses unadjusted survival estimates from TITAN, and uses estimates adjusted for crossover and novel therapy in scenario analyses. We believe, however, that OS and PFS2 adjusted using the 'modified' RPFSTM (and based on the COU-AA-302 trial FA data-cut) would be more appropriate for the main analysis (see TE response Table 41 and the ERG preferred model assumptions in section 3.2 below). We note from the model submitted by the company as part of the TE response that this adjustment was done without re-censoring. The ERG would like to re-iterate that methodological guidance from the NICE DSU recommends re-censoring of adjusted survival estimates.
- Clinical advice to the ERG suggests that the Weibull fits for OS in the ADT alone treatment arm (see TE response Figures 23 and 30 showing non-adjusted and adjusted estimates) underestimate patient survival at 10 and 15 years.
- As for PFS2, the Weibull models for the apalutamide plus ADT arm (shown in TE response Figures 20 and 29) are likely to overestimate progression-free survival at 10 and 15 years. Besides, when these models are selected, patients seem to spend almost no time on third-line treatment. Out of six parametric curves used for extrapolation, the Gompertz models (Figures 20 and 29) seem to be the only alternative that is clinically relevant, although they also are likely to overestimate long-term survival in patients from the active treatment arm. In the ERG base case we use the Gompertz fits and explore the Weibull models in a scenario analysis (see section 3.4 below).
- In the ERG report we suggested that, in such a case, using more flexible modelling approaches (e.g. piecewise) would be more appropriate because the results are sensitive to variations in these estimates.[1]

2.1.2 IPCW adjustment for SPARTAN and TITAN

In TE response Figures 2 and 3, the company provides OS and PFS2 estimates from SPARTAN adjusted using the inverse probability of censored weights (IPCW) approach

along with those from the ITT analysis and censoring analysis. The HRs obtained using IPCW are shown in TE response Tables 9 and 10.

The respective results for TITAN are presented in TE response Figures 4 and 5, and Tables 11 and 12. The company states that the results from the IPCW analyses for both SPARTAN and TITAN illustrate that the assumptions behind this method (related to full adjustment for selection bias induced by artificially censoring patients at time of switch to the second novel therapy) are not fulfilled, because the resulting HR estimates are not clinically plausible (a detailed argument is presented in TE response pages 21-24). The ERG considers this reasonable.

2.2 Issue 2 – Clinical and cost effectiveness of apalutamide in people with mHSPC who are ineligible or unsuitable for docetaxel chemotherapy

The decision problem in the CS includes a sub-group of mHSPC patients 'ineligible or unsuitable for chemotherapy'. An explicit definition of this subgroup is not given in the CS. However, cost-effectiveness estimates are presented separately for mHSPC patients who are:

- Eligible/suitable for docetaxel, for whom the relevant comparison is apalutamide plus ADT versus docetaxel plus ADT, and
- Ineligible/unsuitable for docetaxel, for whom the relevant comparator is apalutamide plus ADT versus ADT.

There is no subgroup analysis in the pivotal TITAN trial for a group of patients specifically defined on the basis of docetaxel eligibility/suitability. Clinical effectiveness estimates for docetaxel ineligible/unsuitable patients treated with apalutamide plus ADT are based on the whole trial population of the TITAN trial. The ERG questions whether the implicit assumption that the results of the whole TITAN trial population can necessarily be applied to patients ineligible/unsuitable to take docetaxel.

The ERG report, therefore, recommends expert clinical opinion to be sought on the feasibility of identifying a sub-group of patients in TITAN with baseline characteristics indicative of docetaxel suitability/eligibility. If it is feasible to define such a group of patients, their survival outcomes could inform an exploratory post hoc subgroup analysis of the clinical

effectiveness of apalutamide plus ADT versus ADT in patients considered ineligible/unsuitable for docetaxel treatment.

In their response the company makes two key points:

- At least three quarters of mHSPC patients are ineligible or unsuitable for chemotherapy. Expert clinical advice to the ERG agrees with this.
- Chemotherapy ineligible/unsuitable patients represent the majority of mHSPC patients. As such, "the efficacy results for apalutamide from TITAN can reasonably be considered no less generalisable than most oncology trials".

The company reiterates their view that docetaxel ineligibility/unsuitability can be affected by multiple factors including age, wellbeing and co-morbidities. They cite other NICE appraisals where attempts have been made to propose such criteria, including TA412 (Radium 223) and the on-going ID945 (abiraterone in treating newly diagnosed high risk mHSPC). For the latter, NHS England have proposed Blueteq criteria for prescribing abiraterone for chemo-ineligible/unsuitable patients with newly diagnosed, high risk, mHSPC, in which patients are classified in terms of those who *cannot*, *should not* or who have *chosen not* to be treated with docetaxel.

The company highlights that this same issue applies to the NICE appraisal of abiraterone (ID945) (NB. Both abiraterone and apalutamide are intended for use at the same position in the care pathway for mHSPC). The issue was one of the points of appeal brought against NICE in September 2020 in the ID945 appraisal. The Appeal Panel upheld the appeal on this point, stating that the appraisal committee could have done further work to explore the possibility of defining a subgroup of patients who are unable or unlikely to receive docetaxel. The issue was discussed at a subsequent Appraisal Committee meeting on the 10th December 2020 (NB. Some of the ERG team for this current appraisal of apalutamide attended the meeting as observers). The outcome of this meeting is not publicly available at the time of writing, however, the company expects the guidance to propose criteria on eligibility and suitability for chemotherapy applicable to mHSPC patients considering treatment with abiraterone. It is likely, therefore, that such criteria would also apply to apalutamide if it were to be approved in the mHSPC population by NICE.

In terms of the TITAN trial, the company cites the consistent OS benefit of apalutamide across the trial's predefined subgroups, and notably the non-statistically significant interaction tests for age and ECOG performance status as providing *"evidence that the*

TITAN trial is applicable to all mHSPC patients, including older patients and those with higher ECOG characteristics that make patients more likely to be ineligible or unsuitable for chemotherapy". The ERG would like to point out the common limitations of subgroup analyses in clinical trials, including lack of sufficient statistical power for some subgroups, and erroneous interpretations of the presence or absence of effect modifiers. Furthermore, it is not clear why only age and ECOG status are selected as indicative of chemotherapy ineligibility/unsuitability in preference to other subgroups (NB. age itself not necessarily an independent predictor, but presumably it has been mentioned as a proxy for frailty and presence of comorbidities which, in turn, are likely to make chemotherapy unsuitable).

ERG conclusion

- The ERG's view is that we can infer the likely generalisability of the TITAN trial to the mHSPC patient population from the consistent effects observed across the OS subgroup analyses. However, the inherent limitations of clinical trial subgroup analyses preclude definitive conclusions about generalisability.
- Any criteria on eligibility and suitability for chemotherapy that may be included in NICE guidance recommending abiraterone for people with newly diagnosed, high risk, mHSPC (ID945) would likely also apply to people considered for treatment with apalutamide. This key issue is therefore contingent on the outcome of ID945.

2.3 Issue 3 – Extrapolation of survival curves: metastatic free survival (MFS) for nmHRPC and radiographic progression free survival (rPFS) for mHSPC

The ERG report notes that the choice of survival extrapolation for MFS/rPFS has a large impact on model results and that there is some uncertainty about the most appropriate model survival curve, particularly for the nmHRPC indication. We recommended that advice should be sought from clinical experts on the most clinically plausible extrapolation distributions for MFS/rPFS.

In their TE response the company reiterates that a wide range of factors were considered when selecting the most appropriate base-case survival curves, including clinical expert opinion. They suggest that the survival extrapolations benefit from the long-term data available from the SPARTAN and TITAN clinical trials *"with median MFS and rPFS outcomes reached for both the apalutamide + ADT and ADT alone arms of each trial at the time of the first data-cut for each study (given median MFS and rPFS were reached at the time of the first data-cut further data was not collected in subsequent data-cuts)."*

We note, however, that the number of patients at risk of the MFS event at the first data cut-(19th March 2017) was zero in both treatment arms of the SPARTAN trial (see CS Figure 10). Similarly, at the first data cut in the TITAN trial (23rd November 2018), no patients were at risk of radiographic progression as shown in CS Figure 23. Therefore, it is not clear what the company meant by "further data" collection, as all patients had either progressed or been censored by these first data cuts.

We would like to reiterate here that, based on clinical advice to the ERG, the parametric models considered by the company underestimate MFS in the ADT arm at 5 and 10 years (except generalised gamma which has a clinically implausible long tail), but are likely to overestimate it in the apalutamide plus ADT arm. As for rPFS, the Weibull fits used in the base case underestimate the proportion of ADT patients radiographic-progression-free at 5, 10 and possibly 15 years.

In our ERG report (though not explicitly included within the key issues for TE) we suggested using more flexible modelling approaches for MFS and rPFS (e.g. piecewise modelling).[1] We note that in the TE response the company did not provide any additional evidence or analysis with regard to this issue.

2.4 Issue 4 – Utility values for second and third-line metastatic hormone relapsed prostate cancer (mHRPC) health states

The company based their values for second and third-line utility on those used in NICE TA387 (Abiraterone for mHRPC not previously treated with chemotherapy) and adjusted these values by applying a relative decline ratio to the utility for first-line mHRPC utility from TA387. In the ERG report we suggested that values from TA387 should be used without adjustment.

The company maintains that their adjustment used to derive second line and third line mHRPC utility values is appropriate on the basis that they follow the recommendations made by NICE DSU TSD 12.[2] In addition, they comment that the estimates used by ERG for the scenario with utility values from TA580[3] (Enzalutamide for nmHRPC) lack clinical validity because the values for second line mHRPC are higher than those for first line mHRPC.

The ERG has the following concerns with the company's adjustment used to derive second line and third line mHRPC utility values:

- The adjusted utility values for second line and third line mHRPC derived by the company are significantly lower than those used in TA377[4] (Enzalutamide for mHRPC) and TA580[3] (Enzalutamide for nmHRPC).
- There is some uncertainty over the estimated values from TA387[5] (Abiraterone for mHRPC) for second line mHRPC as they are not clearly defined as first line, second line or third line mHRPC. We consider that the estimate for the health states 'currently receiving chemotherapy' and 'post-chemotherapy' may be second line mHRPC and these health states have higher utility values than the utility value reported by the company for second line mHRPC (0.625). If these health states are used the utility value for second line mHRPC may be [redacted]
- Applying the adjustment made by the company assumes that utility values will decrease by the same relative proportion as seen between first line to second line mHRPC in TA387, although this may not be the case considering the different starting populations.
- The estimate for third line mHRPC in TA387 has been taken from another study by Sandblom et al,[6] so it is not possible to adjust this value in the same way as has been done for second line.

Given the concerns above, we maintain that the company's adjustment is problematic and it would be better to use the unadjusted utility values from TA377, rather than from TA387. Cost-effectiveness results are presented based on unadjusted utility values from TA387 in a scenario analysis.

2.5 Issue 5 – Market share of subsequent therapies used in metastatic hormone relapsed prostate cancer (mHRPC)

The ERG report highlighted the need for advice from clinical experts on the most clinically plausible estimates of the use of subsequent therapies for mHRPC, specific to patients progressing to mHRPC from nmHRPC and mHSPC, respectively.

In their response the company states that:

- It was assumed that patients in mHRPC received the same set of subsequent therapies after progression from 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.

- The market shares used in the base case were sourced from the mHSPC advisory board.
- The values from the advisory board were applied in the base-case instead of the trial data as this is most reflective of the treatments given to patients in UK clinical practice and accounts for the one novel therapy commissioning policy.
- The values from the mHSPC advisory board were preferred to the nmHRPC advisory board estimates as they provided more up to date estimates given the timing of the advisory boards (June 2019 vs December 2018), because the advisory board consulted a larger number of clinicians (five vs four), and because use of these market share estimates also provided results which were more conservative.

With regard to this issue, the company has not submitted any additional evidence. The ERG has no further comments on this issue.

2.6 Issue 6 – Duration of adverse event costs for docetaxel (mHSPC)

In their response the company agrees with the ERG's view that adverse event costs for docetaxel had been overestimated, however, they suggest that there would be additional adverse event costs related to patient's on-going treatment with ADT after the first six months. Furthermore, they suggest that the docetaxel adverse event rates used in the company's model (reported in the GETUG-AFU 15 clinical trial by Gravis et al. 2013[7]) may potentially be underestimated for neutropenia and febrile neutropenia. They contrast this with real-world data on the use of docetaxel in the NHS reported in Patrikidou et al. 2017[8] showing higher rates. The adverse event rates for Gravis et al. and Patrikidou et al. are shown in Table 2 below.

The ERG notes that the source suggested by the company (Patrikidou et al.)[8] is a letter in the journal Clinical Oncology and the numbers of patients studied are not reported. Furthermore, other real-world evidence cited by the company[9 10] consists of relatively small samples of patients compared to the GETUG-AFU 15 clinical trial by Gravis et al.[7] We note that two other docetaxel clinical trials, CHAARTED (Sweeney et al.[11]) and STAMPEDE (James et al.[12]), reported lower adverse event rates for febrile neutropenia and neutropenia (see Table 2). We pooled the three docetaxel clinical trials (GETUG-AFU 15, STAMPEDE and CHAARTED) and estimated combined rates of 10.6% and 15.4% for febrile neutropenia and neutropenia, respectively. We use these pooled rates in our updated revised base case (see section 3 below).

Table 2 Adverse event rates (grade 3-4) for neutropenia and febrile neutropenia for patients treated with docetaxel

Adverse event rate, Grade 3-4	GETUG-AFU 15 trial Gravis et al. [7] 2013	Real world data Patrikidou et al. 2017[8]	STAMPEDE trial James et al. 2017[12]	CHAARTED trial Sweeney et al. [11] 2016
Number of patients	189	Not reported	550	390
Febrile neutropenia	7%	18.2%	15%	6.1%
Neutropenia	32%	36.3%	12%	12.1%

3. Updated cost-effectiveness results - ERG summary and critique

In their response to TE, the company provided the results of their updated base case analysis, in which they incorporate most of the ERG's preferred assumptions. The company's updated base case includes the following:

- **TITAN trial final data cut**: use of TITAN final analysis results for OS and adverse events.
- **Source of second and third line mHRPC utilities**: adjusted utilities based on TA387 (same as original company's base case).
- **Duration of adverse events costs for docetaxel**: adverse event costs of docetaxel in the first 6 months and adverse event costs associated with ongoing ADT thereafter.
- **Incidence of neutropenia and febrile neutropenia for docetaxel**: 36.3% for neutropenia and 18.2% for febrile neutropenia.

The company has also submitted an updated confidential Patient Access Scheme (PAS) discount on the price of apalutamide of [redacted] (currently subject to approval). Therefore, the company's results presented in their response to TE are based on this proposed PAS price for apalutamide and the list prices for the other treatments included in the model (i.e. those used in subsequent treatment lines). In a separate confidential addendum to this current document we reproduce the company's analyses and the ERG's analyses based on all available the PAS discount prices (i.e. the PAS for apalutamide and PAS discounts for treatments modelled in subsequent lines of therapy).

3.1 Company's revised base case cost-effectiveness results

Table 3 and Table 4 show the company's revised base case results for nmHRPC and mHSPC, respectively. For nmHRPC, the results show that apalutamide plus ADT offers [redacted] of [redacted] and a mean QALY gain of [redacted] compared with ADT alone. Apalutamide plus ADT therefore dominates ADT alone.

Table 3 Company's revised base case results for nmHRPC (discounted, new PAS price for apalutamide)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£/QALY)
ADT alone	[redacted]	5.50	[redacted]				
Apalutamide plus ADT	[redacted]	6.26	[redacted]	[redacted]	0.76	[redacted]	Dominates
Source: reproduced from Table 39 of company's response to technical engagement. ADT: androgen deprivation therapy; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gain; QALYs: quality-adjusted life years.							

For mHSPC, the results show that apalutamide plus ADT offers a [redacted] of [redacted] and a mean QALY gain of [redacted] compared with ADT alone and a [redacted] of [redacted] and a mean QALY gain of [redacted] compared with docetaxel plus ADT. Apalutamide plus ADT therefore dominates both ADT alone and docetaxel plus ADT.

Table 4 Company's revised base case fully incremental results for mHSPC (discounted, new PAS price for apalutamide)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALY	ICER (£/QALY)	ICER (£/QALY): APA vs. ADT
Apalutamide plus ADT	[redacted]	6.375	[redacted]					
ADT	[redacted]	4.664	[redacted]	[redacted]	-1.711	[redacted]		
Docetaxel plus ADT	[redacted]	5.698	[redacted]	[redacted]	1.034	[redacted]	£10,482	Dominates
Source: reproduced from Table 49 of company's response to technical engagement. ADT: androgen deprivation therapy; APA: apalutamide plus ADT; ICER: incremental cost-effectiveness ratio; Incr: incremental; LYG: life years gain; QALYs: quality-adjusted life years.								

3.2 ERG's revised preferred assumptions

We maintain the majority of our original preferred model assumptions (previously discussed in the ERG report). We have only revised our base case to include the following:

- **Apalutamide PAS discount**: [redacted].
- **TITAN data cut for mHSPC**: use of TITAN final analysis data (in agreement with the company's revised base case).
- **Extrapolation of PFS2 for mHSPC**: corrected Gompertz distribution (for further discussion, see key issue 1).
- **Type of crossover and novel therapy adjustment for mHSPC**: 'modified' RPFSTM using final analysis data cut from the COU-AA-302 trial (for further discussion, see key issue 1).
- **Source of second and third line mHRPC utilities**: unadjusted utilities based on the utility values from TA377 (for further discussion, see key issue 4).
- **Duration of adverse events costs for docetaxel for mHSPC**: adverse event costs of docetaxel in the first 6 months and adverse event costs associated with ongoing ADT thereafter (in agreement with the company's revised base case, see key issue 6).
- **Incidence of neutropenia and febrile neutropenia for docetaxel (mHSPC)**: 15.4% for neutropenia and 10.6% for febrile neutropenia (for further discussion, see key issue 6).

3.3 Cost-effectiveness results based on ERG preferred model assumptions

Table 5 and Table 6 show the cumulative cost-effectiveness results of applying the ERG's revised preferred model assumptions and the new apalutamide PAS discount for nmHRPC and mHSPC, respectively.

- For nmHRPC, incorporating the ERG preferred assumptions and the new apalutamide PAS discount reduces the cost of apalutamide plus ADT by £9,060, and apalutamide plus ADT still dominates ADT alone.
- For mHSPC, the ICER decreases from £22,294 per QALY to £7,756 per QALY versus ADT alone. For the comparison against docetaxel plus ADT, apalutamide plus ADT initially had an ICER of £49,298 per QALY, but now apalutamide plus ADT dominates docetaxel plus ADT.
- The changes that have the biggest impact on the cost-effectiveness results are the new apalutamide PAS discount, the use of the Gompertz distribution to extrapolate PFS2 and the use of TITAN final analysis data.
- Incorporating the remaining ERG assumptions influences the ICERs to a lesser extent.

Table 5 Cumulative cost-effectiveness results for ERG's revised preferred model assumptions for nmHRPC (discounted, new PAS price for apalutamide)

Parameter	Treatment	Total costs	Total QALYs	ICER (£/QALY)
ERG original base case	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Apalutamide PAS discount: [redacted]	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
+ Source of 2L/3L mHRPC utilities: TA377 (corrected)	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates
ERG revised preferred base case	ADT alone	[redacted]	[redacted]	
	APA+ADT	[redacted]	[redacted]	Dominates

2L: second line, 3L: third line; ADT: androgen deprivation therapy; APA: apalutamide; ERG: evidence review group; ICER: incremental cost-effectiveness ratio; mHRPC: metastatic hormone relapsed prostate cancer; QALY: quality-adjusted life-years.

Table 6 Cumulative cost-effectiveness results for ERG's preferred model assumptions for mHSPC (discounted, new PAS price for apalutamide)

Scenario	Treatment	Total costs	Total QALYs	ICER (£/QALY)	
				APA vs. DOX	APA vs. ADT alone
ERG original base case	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£49,298	£22,294
+ Apalutamide PAS discount: [redacted]	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	£23,143	£9,604
TITAN data cut-off: final analysis (unadjusted)	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	Dominates	Dominates
+ PFS2 extrapolation: jointly fitted corrected Gompertz	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	Dominates	Dominates
+ Type of novel therapy/crossover adjustment: RPFSTM FA	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	Dominates	£7,822
+ Source of 2L/3L mHRPC utilities: TA377 (corrected)	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	Dominates	£7,756
+ Docetaxel AE costs (ERG TE)	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	Dominates	£7,756
ERG revised preferred base case	ADT alone	[redacted]	[redacted]		
	DOX+ADT	[redacted]	[redacted]		
	APA+ADT	[redacted]	[redacted]	Dominates	£7,756

2L: second line, 3L: third line; ADT: androgen deprivation therapy; AE: adverse event; APA: apalutamide; DOX: docetaxel; ERG: evidence review group; ICER: incremental cost-effectiveness ratio; mHRPC: metastatic hormone relapsed prostate cancer; PFS2: secondary progression free survival; QALY: quality-adjusted life-years; RPFSTM: Rank Preserving Structural Failure Time Model.

3.4 Scenario analyses conducted on the ERG's revised preferred assumptions

We performed a range of scenario analyses with the ERG revised base case to assess the impact of changing the following model assumptions:

- Use different approaches to adjust survival estimates for trial crossover and use of more than one novel therapy.
- Use dependently fitted curves with the Weibull distribution to extrapolate PFS2 for mHSPC.
- Apply adjusted utility values for second and third line mHRPC health states (company's original assumption).
- Use alternative sources to estimate utility values for second and third line mHRPC health states (TA387).
- Apply the incidence of neutropenia and febrile neutropenia used by the company in response to TE (36.3% and 18.2% respectively).

Table 7 presents the results for nmHRPC and Table 8 for mHSPC. The ERG notes:

For nmHRPC

- Apalutamide plus ADT dominates ADT alone in all the scenarios performed.

For mHSPC

- Apalutamide plus ADT dominates ADT alone only when there is no adjustment for novel therapy/crossover. In the remaining scenarios, the ICER change from £1,994 per QALY (scenario: use of Weibull to extrapolate PFS2) to £11,688 (scenario: use of IPCW approach to adjust for novel therapy/crossover).
- Apalutamide plus ADT dominates docetaxel plus ADT in all the scenarios performed.

Table 7 Scenario analyses using the ERG's revised base case for nmHRPC (discounted, new PAS price for apalutamide)

Scenario	ICER (£/QALY)
ERG revised preferred base case	Dominates
Type of novel therapy/crossover adjustment: unadjusted	Dominates
Type of novel therapy/crossover adjustment: 'modified' RPFSTM IA3	Dominates
Type of novel therapy/crossover adjustment: IPCW	Dominates
2L/3L mHRPC utility values: with company adjustment	Dominates
2L/3L mHRPC utility values from TA387	Dominates
2L: second line; 3L: third line; ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; IPCW: inverse of the probability of censoring weights; mHRPC:	

metastatic hormone resistant prostate cancer; nmHRPC: non metastatic hormone resistant prostate cancer; QALYs: quality-adjusted life years, RPFSTM: Rank Preserving Structural Failure Time Model.

Table 8 Scenario analyses using the ERG's revised base case for mHSPC (discounted, new PAS price for apalutamide)

Scenario	ICER (£/QALY) vs. DOX	ICER (£/QALY) vs. ADT alone
ERG revised preferred base case	Dominates	£7,756
Type of novel therapy/crossover adjustment: unadjusted	Dominates	Dominates
Type of novel therapy/crossover adjustment: 'modified' RPFSTM IA3	Dominates	£7,756
Type of novel therapy/crossover adjustment: IPCW	Dominates	£11,688
PFS2 extrapolation: jointly fitted Weibull	Dominates	£1,994
2L/3L mHRPC utility values: with company adjustment	Dominates	£7,880
2L/3L mHRPC utility values from TA387	Dominates	£7,822
Incidence of neutropenia and febrile neutropenia for docetaxel: 36.3% and 18.2%, respectively	Dominates	£7,756

2L: second line; 3L: third line; ADT: androgen deprivation therapy; AE: adverse event; DOX: docetaxel plus ADT; ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; IPCW: inverse of the probability of censoring weights; mHSPC: metastatic hormone sensitive prostate cancer; mHRPC: metastatic hormone resistant prostate cancer; PFS2: secondary progression free survival; QALYs: quality-adjusted life years; RPFSTM: Rank Preserving Structural Failure Time Model.

4. Appendices

Appendix 4.1 Final results from the TITAN trial - ERG summary and critique

Interim results from TITAN were provided in the CS based on a clinical data cut on 23rd November 2018. The company provide results from the final data cut (up to 7th September 2020) for selected outcomes in section 7 of their response to technical engagement (NB. The ERG has not been provided with an updated clinical study report). The median duration of follow-up for this update is [redacted] months longer than median follow-up for the interim analysis presented in the CS. An overview of the TITAN trial outcome measures and data cuts is presented in Table 9. The ERG notes that the CS section B.2.4 indicates that a second interim analysis for OS was planned. The ERG assumes that this second interim analyses was not required/performed.

Table 9 TITAN data cuts and outcome measures

Outcome measure	Status of trial data cut as reported in:	
	CS (July 2020) & response to clarification questions (September 2020)	Company's response to Technical engagement (January 2021)
Co-primary efficacy outcomes		
Radiographic progression-free survival (rPFS)	Final	N/A
Overall survival (OS)	1st interim	Final
Secondary outcomes		
Time to cytotoxic chemotherapy	1st interim	Final
Time to pain progression	1st interim	Final
Time to chronic opioid use	1st interim	Final
Time to skeletal-related event	1st interim	Final
Exploratory outcomes		
Time to progression on first subsequent therapy (PFS2)	1st interim	Final
Time to PSA progression	1st interim	NR
Best overall response	1st interim	NR
Other outcomes		
Health-related quality of life	1st interim	NR
Adverse events	1st interim	Final

N/A = Not applicable; NR = Not reported

4.1 Updated efficacy results

The outcomes rPFS, PFS2 and OS inform the economic model. Final results for the co-primary outcome rPFS were included in the CS and therefore have not been updated.

Updated results for the co-primary outcome OS and the exploratory outcome of PFS2 are described below.

4.1.1 Overall survival (OS)

Final results for the OS outcome are presented in Table 15 of the TE response:

- The updated HR for OS (HR: [redacted]) is consistent with the interim HR but has narrower 95% confidence interval due to the longer period of follow up (Table 10).

For the co-primary outcome of OS, n=[redacted] deaths were required to detect a HR of 0.75 (with 80% power and two-sided alpha of 0.045; CS Table 9). The updated TITAN analysis reports a slightly lower number of deaths (n=[redacted]) but this is unlikely to have a significant impact on study power.

The company provide an updated assessment indicating that the assumption of proportional hazards holds for the updated final analysis for OS (Figures 10 and 11 of TE Response). The ERG agrees with this conclusion based on visual inspection of the plots.

4.1.2 PFS2 (exploratory outcome)

Final results for the exploratory PFS2 outcome are presented in Table 48 of the TE response:

- The updated HR for PFS2 [redacted] is consistent with the interim HR and has a narrower 95% confidence interval due to the longer period of follow up (Table 10 of this document).

The results for PFS2 in Table 10 are based on original trial censoring rules whereby patients were censored at the last known date alive or at the start of a second subsequent therapy. The company explains that they have used an alternative unadjusted estimate for PFS2 for the base case using alternative censoring rules, whereby patients were not censored at the start of a second subsequent therapy (page 119 and Table 48 of TE Response). (NB. The ERG assumes there is a typographical error in the footnote of the third column of Table 48 and that this alternative censoring method means that deaths after the start of a second subsequent therapy are also included (as indicated by footnote to Table 8 of the TE response)). The company reports that this was to ensure the PFS2 KM curve remained above the OS KM curve in order to preserve the structural integrity of the partition model used in the economic analysis:

- This alternative PFS2 estimate [redacted] is generally consistent with that obtained with the original trial censoring rules, though the confidence interval is narrower.

The company provide an updated assessment indicating that the assumption of proportional hazards holds for the updated final analysis for PFS (Figure 19 of TE response). The ERG agrees with this conclusion based on visual inspection of the log cumulative hazard plot.

Table 10 Comparison of interim and final results from TITAN (original trial censoring rules).

Analysis	**Interim**		**Final**	
Source	CS and company response to clarification questions		Technical engagement response form	
Analysis cut-off date	23rd November 2018		7th September 2020	
Median follow-up	22.7 months		[redacted]	
No. (%) of patients switching from placebo to apalutamide	Not reported (as not available)		[redacted]	
Efficacy results	**Apalutamide plus ADT**	**Placebo plus ADT**	**Apalutamide plus ADT**	**Placebo plus ADT**
No. randomised	525	527	525	527
No. alive after treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
No. (%) who received subsequent therapy [a] after discontinuation from study treatment	[redacted]	[redacted]	[redacted]	[redacted]
rPFS				
Events	[redacted]	[redacted]	No update	
Median survival in months (95% CI)	[redacted]	[redacted]		
HR (95% CI)	[redacted]			
PFS2				
Events	88	121	[redacted]	[redacted]
Median survival in months (95% CI)	NE (NE; NE)	NE (NE; NE)	[redacted]	[redacted]
HR (95% CI)	0.66 (0.50 to 0.87)		[redacted]	
OS				
Events	83	117	[redacted]	[redacted]
Median survival in months (95% CI)	NE (NE; NE)	NE (NE; NE)	[redacted]	[redacted]
HR (95% CI)	0.67 (0.51 to 0.89)		[redacted]	

[a] Life-prolonging therapies; denominator is number of pts alive after treatment discontinuation

[b] Not adjusted for crossover or subsequent therapy

4.1.3 Patient crossover and treatment switching

Page 43 ('Patient disposition and treatment exposure' sub-section) and Table 16 of the TE response, respectively, provide details of the number of patients who crossed over from placebo to apalutamide treatment following unblinding of the trial, and the numbers who received life-prolonging subsequent therapies after discontinuing their respective randomised treatments:

- [redacted] of patients in the placebo plus ADT arm switched to the active trial arm following unblinding at the time of the interim analysis (see Table 10 of this document).
- The proportion of patients in the placebo plus ADT arm who received a life-prolonging subsequent therapy [redacted] was higher than that in the active arm [redacted], which is consistent with that observed in the interim analysis (Table 10).

As discussed in the ERG report, crossover and treatment switching may introduce bias in the estimates of treatment effect for longer term survival outcomes (PFS2 and OS). Methods to adjust for crossover and subsequent therapy are discussed in section 2.1 of this document. The company have chosen to use unadjusted estimates for the economic model base case as these are more conservative than adjusted estimates.

4.1.4 Subgroup analysis

Updated predefined subgroup analyses for OS are provided in Figures 6 and 8 of the company's response to technical engagement:

- In general, the updated results are consistent with the observations from the interim analysis.
- The point estimates for the treatment effect of apalutamide on OS [redacted]

4.1.5 Secondary and other outcomes

Updated results for secondary outcomes are presented in Table 17 of the company's TE response.

- These are broadly similar to the interim results (CS section B.12.2) and are not further elaborated in this document as they do not inform the economic model.

Health-related quality of life outcomes were presented in the CS but have not been updated in the TE response, however, these do not inform the economic model.

4.1.6 Updated safety results

4.1.6.1 Treatment exposure

Median treatment exposure (Table 11) is reported for each treatment arm and for the crossover group; the proportion of patients still receiving treatment is reported for the apalutamide plus ADT arm and the crossover group. However, the proportion of patients requiring dose reductions or dose interruptions is not reported.

Table 11 Treatment exposure in the TITAN safety population

	Interim Analysis		Final Analysis		
Source	CS and company response to clarification questions		TE response form		
	Apalutamide plus ADT N=524	**Placebo plus ADT N=527**	**Apalutamide plus ADT N=524**	**Placebo plus ADT N=527**	**Crossover group N=208 [a]**
Median treatment exposure (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients still receiving treatment	[redacted]	[redacted]	[redacted]	[redacted]NR	[redacted]
Proportion of patients requiring dose reductions	[redacted]	[redacted]	[redacted]NR	NR	[redacted]NR
Proportion of patients requiring dose interruptions	[redacted]	[redacted]	[redacted]NR	[redacted]NR	[redacted]NR

[a] comprising [redacted]% of patients randomised to placebo plus ADT; NR: Not reported

4.1.6.2 Summary of adverse events

The company states that safety results from the final analysis are consistent with those presented in the interim analysis, and provide two tables of data to support this:

- Table 18, an overall summary of TEAEs and SAEs in the safety population that is directly comparable with summary Table 46 in the CS.
- Table 19, reporting the number of subjects with TEAEs (in the safety population) with frequency of at least 10% in any Treatment Group by System Organ Class and Preferred Term that is directly comparable with Table 23 in the Interim CSR for TITAN.

Table 12 below combines summary data of TEAEs and SAEs in the safety population from the interim analysis and the final analysis. It shows that:

- safety data are consistent for the placebo arm.
- safety data are consistent for the apalutamide arm, except that,
- there is an increase in the proportion of TEAEs at Grade 3-4 (increase of 7.2 percentage points), the total proportion of SAEs (increase of 9.4 percentage points) and the proportion of SAEs at Grade 3-4 (increase of 7.7 percentage points). The ERG does not regard this as significant, especially as the increase does not affect the proportion of drug-related adverse events.

Table 12 Summary of adverse events (safety population)

	Interim Analysis		Final Analysis	
	Apalutamide plus ADT (n = 524)	**Placebo plus ADT** (n = 527)	**Apalutamide plus ADT** (n = 524)	**Placebo plus ADT** (n = 527)
TEAEs, total, n (%)	507 (96.8)	509 (96.6)	[redacted]	[redacted]
TEAEs, drug-related, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs, Grade 3-4, n (%)	221 (42.2)	215 (40.8)	[redacted]	[redacted]
TEAEs, Grade 3-4, drug-related, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
SAEs, total, n (%)	104 (19.8)	107 (20.3)	[redacted]	[redacted]
SAEs, drug-related, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
SAEs, Grade 3-4, n (%)	84 (16.0)	86 (16.3)	[redacted]	[redacted]
TEAE-related discontinuation, n (%)	42 (8.0)	28 (5.3)	[redacted]	[redacted]
TEAE-related discontinuation, drug-related, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
TEAE-related deaths, n (%)	10 (1.9)	16 (3.0)	[redacted]	[redacted]
TEAE-related deaths, drug-related, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Deaths within 30 days of last dose, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Death due to prostate cancer, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Death due to AE, n (%)	10 (1.9)	16 (3.0)	[redacted]	[redacted]

Source: CS Table 46 and TE response table 18

AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event

The ERG compared TE response table 19 with the Interim CSR Table 23 and can confirm that the safety data is consistent according to TEAEs by system organ class.

Adverse events of special interest (AESI)

The AESIs identified for TITAN in the CS were skin rash, fall, fracture, and hypothyroidism.

- Skin rash merited discussion in the CS. In the TE response, Table 19 reports rash as occurring in [redacted] of patients in the apalutamide plus ADT arm, and pruritis as occurring in [redacted] of patients in the apalutamide plus ADT arm.
- Rash and pruritus were more frequently reported in the intervention arm than in the placebo arm in both interim and final analyses.
- Skin rash frequency has increased slightly by 4.9 percentage points in the apalutamide plus ADT arm since the interim analysis.
- The TE response does not specify at what severity grades the adverse events of rash occurred ([redacted] from the interim analysis).

ERG conclusion

The efficacy data (PFS2 and OS) and safety evidence (numbers of TEAEs and SAEs) reported in the TE response are consistent with the evidence reported from the interim analysis in the original company submission. However, the TE response does not discuss AESIs, especially skin rash and ischaemic heart disease, nor report proportions of patients requiring dose reductions or dose interruptions.

Appendix 4.2 Updated results from network meta-analysis - ERG summary and critique

An updated NMA was presented by the company to include the final data cut of the TITAN trial for the OS and safety (adverse events [AEs] and serious adverse events [SAEs]) endpoints.

For OS the company chose the fixed effect model as their base case (as they did in the original NMA) and presented two sensitivity analyses using random effects models with different prior distributions (Table 23 of the TE response document). We compare the results of these with the results of the original NMA presented in the CS (based on interim OS data from TITAN) (Table 13).

Table 13 NMA OS results from company submission and updated with final TITAN data cut

Comparison		OS original base case FE	OS updated base case FE	OS updated sensitivity analysis RE models (u[0,1])	OS updated sensitivity analysis RE models (u[0,0.4])
Apalutamide plus ADT vs ADT alone	HR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]
	Probability that HR is less than 1	[redacted]	[redacted]	[redacted]	[redacted]
Apalutamide plus ADT vs docetaxel plus ADT	HR (95% CrI)	[redacted]	[redacted]	[redacted]	[redacted]
	Probability that HR is less than 1	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; CrI, credible interval; FE, fixed effects; HR, hazard ratio; NMA, network meta-analyses; OS, overall survival; RE, random effects

[redacted] This reflects the slight improvement in OS observed in the final TITAN data cut as we reported earlier (Appendix 4.1). The ERG reran the updated OS NMA and obtained the same results as the company. The company prefers the fixed effect model, whilst the ERG prefers a random effects model with a Uniform(0,1) informative prior. Note: the mean estimates for fixed and random effects are the same so this will only impact any

probabilistic sensitivity analyses. We also concur with the company that the proportional hazards assumption still holds for OS (Figures 10 & 11 of the company TE responses). However, we note that the final OS data included in the NMA does not adjust for crossover from placebo plus ADT to apalutamide plus ADT and hence the results of the NMA should be viewed as conservative.

We also note the proportion of patients receiving subsequent therapies has changed in the final analysis. The apalutamide plus ADT arm has increased from 17% to [redacted] and the placebo plus ADT arm has increased from 36% to [redacted] (Table 21 TE responses). However, we note the N and proportion receiving subsequent therapies in the apalutamide plus ADT arm at the interim analysis in Table 21 (N=87 and 17%) does not agree with the interim analysis from Table 39 (CS document B) which put these figures at N=190 and 36%, respectively. Nonetheless, with a higher proportion of patients in the placebo plus ADT arm receiving subsequent therapies (particularly abiraterone and enzalutamide) we would expect those patients to received greater benefit and therefore this to be conservative for the analysis.

The ERG was unable to validate the company's updated safety outcomes results, particularly SAE which were used in the economic model.

Firstly, whether the analysis includes all SAEs or is restricted to grade 3-4 SAEs is unclear.

- The model suggests grade 3-4 SAEs (worksheet "AE Costs", cell B46) but this is not supported by the text or tables in the CS (p142, Table 42).

Secondly, the data and studies contributing to the analysis is unclear.

- The CS (p139) and Table 38 state three studies report data on SAEs to be included in the analysis: TITAN; STAMPEDE IPD; and GETUG-AFU15. However, this is contrasted by Table D.50 in the appendix which has omitted GETUG-AFU15.
- This inconsistency is also borne out in the company's TE response Table 20, hence we are unclear whether GETUG-AFU15 has been excluded from the updated analysis.
- Furthermore, no data for the STAMPEDE (IPD) nor GETUG-AFU15 trials are reported.

Nevertheless, the ERG acknowledges that SAEs have a very limited impact on the ICER (<£5).

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