NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Abiraterone (originator and generics) for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer (review of TA721) [ID6378]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

COST COMPARISON APPRAISAL

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Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **NICE medicines optimisation team (MOT) report**

2. **Patient group, professional group, and NHS organisation submission** from:
   a. Prostate Cancer Research
   b. Prostate Cancer UK
   c. Tackle Prostate Cancer

3. **Expert personal perspectives** from:
   a. Professor Alison Birtle, consultant oncologist – clinical expert, nominated by NICE
   b. Ellie Blake, senior policy officer – patient expert, nominated by Prostate Cancer UK
   c. Dr Stephen Allen, patient representative – patient expert, nominated by Tackle Prostate Cancer

4. **External Assessment Report** prepared by PenTAG

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Abiraterone for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer in adults [ID6378]

NICE medicines optimisation briefing

March 2025

Key issues

- Abiraterone is an anti-androgen licensed in newly diagnosed high-risk hormone-sensitive metastatic prostate cancer. However, other anti-androgens are licensed in all people with hormone-sensitive metastatic prostate cancer.
- Enzalutamide and apalutamide are also anti-androgens. However, abiraterone has a different mechanism of action to the other medicines.
- Adverse event profiles (including for falls, fractures, cognitive impairment, and seizures) differ between treatment options. The person's risk of these adverse events, and their values and preferences, should therefore be taken into account.
- Concomitant prednisolone is needed with abiraterone but not enzalutamide or apalutamide.

Technology overview

Abiraterone is an androgen biosynthesis inhibitor licensed for treating newly diagnosed high-risk metastatic hormone-sensitive prostate cancer in adults in combination with androgen deprivation therapy (summary of product characteristics [SPC] for abiraterone [Zytiga] and multiple generic products).

Context

Abiraterone with prednisone or prednisolone plus androgen deprivation therapy for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer was assessed by NICE in 2021 (TA721). Abiraterone was not recommended for use within the NHS because, whilst clinical trial results showed that abiraterone was clinically effective, it was not cost-effective. Since publication of the technology appraisal, several generic versions of abiraterone have become available. Prednisone is no longer available in the UK.

In December 2024, NHS England published an interim commissioning policy recommending abiraterone and prednisolone for newly diagnosed high-risk hormone-sensitive metastatic prostate cancer. Newly diagnosed high-risk hormone-sensitive metastatic prostate cancer is classified as having at least 2 of the following factors:

- a Gleason score of ≥ 8
- presence of ≥ 3 bone metastases on conventional imaging (CT scan or isotope bone scan)
- the presence of visceral metastasis on conventional imaging (CT scan) (excluding lymph node disease).

NICE has also assessed enzalutamide and apalutamide (both with androgen deprivation therapy) for treating hormone-sensitive metastatic prostate cancer (TA712 and TA741, respectively). Enzalutamide is recommended as an option. Apalutamide is only recommended if docetaxel is unsuitable. Darolutamide with androgen deprivation therapy and docetaxel is also recommended as another treatment option (TA903). All of these options are recommended in all people with hormone-sensitive metastatic prostate cancer whereas abiraterone is only licensed in newly diagnosed high-risk hormone-sensitive metastatic

prostate cancer. A technology appraisal for darolutamide with androgen deprivation therapy, but without docetaxel, is in development (ID6452).

NICE has published guidance on the diagnosis and management of prostate cancer (NG131).

Table 1: Characteristics of abiraterone compared with other treatments used for newly diagnosed high-risk hormone-sensitive metastatic prostate cancer at a similar point in the treatment pathway (different mechanisms of action)

	Abiraterone (with prednisolone and androgen deprivation therapy)	**Enzalutamide (with androgen deprivation therapy)**	**Apalutamide (with androgen deprivation therapy)**
Mechanism of action	Androgen biosynthesis inhibitor. Selectively inhibits the enzyme 17α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in and is needed for androgen biosynthesis in testicular, adrenal and prostatic tumour tissues.	Potent androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. Competitively inhibits androgen binding to androgen receptors.	Selective androgen receptor inhibitor.
Indication	Treating newly diagnosed high-risk metastatic hormone-sensitive prostate cancer in adults in combination with androgen deprivation therapy and prednisolone (SPC).	Treating metastatic hormone-sensitive prostate cancer in adults in combination with androgen deprivation therapy (SPC).	Treating metastatic hormone-sensitive prostate cancer in adults in combination with androgen deprivation therapy (SPC).
NICE recommendation	Abiraterone with prednisone or prednisolone plus androgen deprivation therapy is not recommended, within its marketing authorisation, for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer in adults (TA721).	Enzalutamide plus androgen deprivation therapy is recommended, within its marketing authorisation, as an option for treating hormone-sensitive metastatic prostate cancer in adults (TA712).	Apalutamide plus androgen deprivation therapy is recommended as an option for treating hormone-sensitive metastatic prostate cancer in adults only if docetaxel is not suitable (TA741).
Dosage and route of administration	1,000 mg (two 500 mg tablets) as an oral single daily dose with 5 mg prednisone or prednisolone daily.	160 mg (four 40 mg tablets) as an oral single daily dose.	240 mg (one tablet) as an oral single daily dose.

	Medical castration with a luteinising hormone-releasing hormone analogue should be continued during treatment in people who have not had surgical castration.	Medical castration with a luteinising hormone-releasing hormone analogue should be continued during treatment in people who have not had surgical castration.	Medical castration with a luteinising hormone-releasing hormone analogue should be continued during treatment in people who have not had surgical castration.
Resource impact	Oral treatment: convenient, non-invasive.	Oral treatment: convenient, non-invasive.	Oral treatment: convenient, non-invasive.

Current practice

Medicines for treating metastatic prostate cancer are commissioned by NHS England. Usual treatment for hormone-sensitive metastatic prostate cancer always includes androgen deprivation therapy, which may be given alone, or with:

- docetaxel with or without prednisolone,
- enzalutamide,
- apalutamide, or
- darolutamide with docetaxel.

Abiraterone with prednisolone and androgen deprivation therapy would be another treatment option.

System intelligence from NICE associates indicates that local treatment pathways follow NICE guidance and that abiraterone would be used at the same place in the treatment pathway as enzalutamide, apalutamide (where docetaxel is unsuitable), or darolutamide with docetaxel. Abiraterone is accepted for use within NHS Scotland for treating newly diagnosed high-risk metastatic hormone-sensitive prostate cancer (Scottish Medicines Consortium: abiraterone acetate) and is recommended by the European Society for Medical Oncology (ESMO) as a first-line option for hormone-sensitive metastatic prostate cancer with androgen deprivation therapy (ESMO Clinical Practice Guidelines - prostate cancer).

Patient centred factors

Abiraterone, like enzalutamide and apalutamide, is another option for people with hormone-sensitive metastatic prostate cancer, especially for people who cannot have docetaxel or choose not to have docetaxel.

NHS England's docetaxel commissioning policy states that docetaxel should not be used in people with a poor overall performance status

(World Health Organization performance 3 to 4), pre-existing peripheral neuropathy, poor bone marrow function, or a life-limiting illness. Therefore, abiraterone, enzalutamide and apalutamide, may be preferred options for people who are unable to have docetaxel.

Abiraterone can cause hypertension, hypokalaemia and fluid retention because of increased mineralocorticoid levels resulting from CYP17 inhibition. Therefore, caution is needed in people whose underlying medical conditions might be affected by these adverse events (SPC). To reduce these effects, abiraterone is given with prednisolone. Concomitant prednisolone is not needed with enzalutamide or other anti-androgens. Therefore, enzalutamide or apalutamide may be preferred options for people who are unable to or do not want to take corticosteroids, for example because of diabetes and the risk of hyperglycaemia, or because of other corticosteroid-related adverse events or the increased pill burden. Prednisolone also requires additional baseline assessments and ongoing monitoring.

Adverse event profiles (including for falls, fractures, cognitive impairment, and seizures) differ between treatment options. The person's risk of these adverse events, and their values and preferences, should therefore be taken into account. Concomitant enzalutamide or apalutamide with coumarin-like anticoagulants should be avoided; therefore abiraterone may be a preferred option for people taking coumarin-like anticoagulants.

Health inequalities

The choice and treatment options for all patients should take into account a person’s values and preferences along with their clinical conditions and suitability for different treatment options.

Prostate cancer is more common in people of Black African ethnicity, people with a family history of prostate cancer and people with a

homologous recombination repair mutation. People of Ashkenazi Jewish ethnicity have a greater risk of having a BRCA gene mutation and so have a higher risk of developing prostate cancer (TA951).

As in previous appraisals for technologies for treating prostate cancer, recommendations should apply to trans women as well as to men.

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Patient Organisation Submission

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 Research
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Prostate Cancer Research (PCR) is a research and patient engagement organisation focused on advancing ground-breaking research and interventions into diagnosis, treatment, and care to create a future where prostate cancer no longer threatens lives. Our focus is on delivering innovative solutions and improving quality of life for patients, families, and communities affected by prostate cancer, and supporting and encouraging marginalised and underrepresented communities to be part of the positive changes we are working to achieve in research, treatment and care. To achieve this, our team of 38 members of staff are focused on four core programmes of work: • Academic and social research funding aimed at groundbreaking advances in preventing, diagnosing, and treating advanced prostate cancer and enhancing patient quality of life; • Translational research, bridging the gap between industry, investors, health providers, and patients, supporting diagnostics and treatments to progress from laboratory to patient; • Patient information and empowerment, giving marginalised and traditionally underrepresented individuals with prostate cancer a greater role in shaping research, treatment, and care; • Policy and advocacy, seeking to ensure greater equity of treatment and parity of care, and working towards a world where no one affected by prostate cancer is left behind PCR's work is funded through diverse income streams. We are focused on accessing significant restricted funding through Trusts & Foundations, Statutory, Corporates and Major Donors, while at the same time

	ensuring we have flexible and sustainable funding through our Events & Community, Legacies and Individual Giving fundraising. PCR is not a membership organisation but works with thousands of patients across its various charitable activities. In the two years since we launched the infopool, an educational website to support and empower patients, we have had close to 250,000 visitors. Since launching Prostate Progress, our patient data platform, in July 2024 we have over 4,000 consented patients signed up to the platform sharing PROMs data and consenting to link their clinical data.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	In the past 12 months, PCR has received funding from the following: • Astellas: £1,096 received for speaker services at a healthcare professional focused event • AstraZeneca: £15,000 received through an educational grant for a report into the socio-economic impact of prostate cancer screening, and £36,000 received in sponsorship of our 'Empowering Communities' project, to assist in evidence generation and intervention co-design with the Black community • Bayer: £83,710 received for an Institute Sponsored Collaborative Study into identifying and assessing regional variation in prescribing practices for hormone therapy and docetaxel, and £1,260 received for speaker services related to a health inequalities roundtable • Ipsen: £5,000 received through an educational grant for a report into the socio-economic impact of prostate cancer screening • Johnson & Johnson Innovative Medicines: £1,265 received for membership of the steering committee for a real-world evidence project.
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 carers to include in your submission?	For personalised information and support, the infopool offers resources tailored to individuals living with prostate cancer. This platform provides insights into treatment options, side effect management, and personal stories from others navigating similar experiences. Patient stories collected through the infopool give valuable

	insights into patient experience and preferences. We have over 1,000 stories from individuals on the site which have helped inform our submission. Additionally, we conducted an online 'Patient Experience Survey' hosted on PCR's website for a period of two weeks in January 2022. The aim of this survey was "To better understand patients' disease journeys, information needs and impact on their quality of life." Insights from this survey have also informed our submission.

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?	Living with hormone-sensitive metastatic prostate cancer (mHSPC) means facing the challenges of both the disease itself and the side effects of its treatment. At this stage of the disease, treatment can no longer aim to cure the cancer, which can be a difficult reality for people whose disease has progressed. For those diagnosed late, when the cancer has already spread, there's also the added impact and frustration of not having had the chance of earlier diagnosis. While androgen deprivation therapy (ADT) can be effective for a period of time, it often comes with a range of side effects, including hot flashes, tiredness, loss of muscle and bone strength, sexual difficulties, and an increased risk of conditions like diabetes and heart disease. Beyond the physical effects, the emotional and psychological impact of mHSPC can be significant. Many patients experience feelings of anxiety, sadness, or depression as they adjust to life with cancer and its treatment. The disease doesn't just affect those diagnosed – it also has a profound impact on family members and loved ones.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients with prostate cancer value and appreciate access to effective treatments as well as the care and support they receive from NHS oncology teams, urologists, specialist nurses and GPs. They value being able to access oral treatments that can be taken at home. However, many feel frustrated that treatment choices are limited and would like more flexibility to personalised care based on side effects, lifestyle or preferences. Some patients report that care can feel disjointed, and their mental health and sexual function needs have been overlooked. There is also a widespread frustration in England and Northern Ireland about the unavailability of certain drugs that are available to men in Scotland and Wales.
8. Is there an unmet need for patients with this condition?	Abiraterone directly addresses several of the most important unmet needs in the treatment of mHSPC – improving survival, delaying disease progression, minimising side effects, and expanding treatment options. It's important to recognise that not every patient with mHSPC is the same. Newly-diagnosed mHSPC patients are currently offered several options: ADT alone; docetaxel plus ADT; docetaxel plus darolutamide and ADT; enzalutamide and ADT; apalutamide plus ADT. The choice of which of these options a patient receives depends on a number of issues, such as the wishes and fitness of the patient, any relevant comorbidities and concurrent medications that may make some options unsuitable, and on the differing licensing conditions of the androgen receptor inhibitors in mHSPC. According to NHS England, approximately 5,200 mHSPC patients per year receive current commissioned first-line treatments of enzalutamide or apalutamide, with 30% of these patients (1,560) estimated to benefit from abiraterone per year in England.[1]

[1] https://www.england.nhs.uk/publication/abiraterone-acetate-and-prednisolone-for-high-risk-hormone-sensitive-metastatic-prostate-cancer-adults-2424/

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	This importantly offers a different treatment option for patients that has been shown to be effective for some patients. Abiraterone works in a different way to the androgen receptor inhibitors, blocking the production of testosterone from the testicles, adrenal glands, and the tumour. As highlighted by NICE in their original review of this technology, abiraterone in combination improved both progression-free and overall survival compared with ADT alone in trial data from LATITUDE and STAMPEDE, and progression-free survival compared with docetaxel in combination. This has since been strengthened by extended analysis data following up patients in the STAMPEDE trial in 2022.[2]

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Abiraterone is generally tolerated well by patients, there are a number of common side effects that patients that have received abiraterone have spoken about to us from their own experiences – including physical and mental fatigue, neuropathic pain, and hot flushes. Some of these side effects are mitigated by the accompanying prednisolone.

[2] James ND, Clarke NW, Cook A et al; STAMPEDE Trials Collaborative Group. Abiraterone acetate plus prednisolone for metastatic patients starting hormone therapy: 5-year follow-up results from the STAMPEDE randomised trial (NCT00268476). Int J Cancer. 2022 Aug 1;151(3):422-434. doi: 10.1002/ijc.34018.

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.	As highlighted by NHS England's interim clinical commissioning policy, abiraterone could benefit patients with two of the following factors: • a Gleason score of ≥ 8 • presence of ≥ 3 bone metastases • the presence of visceral metastasis (excluding lymph node disease) This could be particularly beneficial to those patients that opt not to receive chemotherapy. Many patients may also be unable to receive chemotherapy based on their age or comorbidities they may have, and abiraterone provides an alternative option for these patients.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No

Other issues

13. Are there any other issues that you would like the committee to consider?	No

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Living with hormone-sensitive metastatic prostate cancer means facing the challenges of both the disease itself and the side effects of its treatment – not only the physical effects, but also the significant emotional and psychological impact. • Abiraterone directly addresses several of the most important unmet needs in the treatment of mHSPC – improving survival, delaying disease progression and expanding treatment options for patients, particularly for those who may be unable to tolerate chemotherapy. • Abiraterone offers patients with mHSPC the hope of living longer with stable disease, by improving progression-free survival and delaying the time to disease progression. • Patients in England and Northern Ireland feel that it is unfair that certain treatments are unavailable to them but are available to their counterparts in Scotland and Wales.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

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- 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	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Prostate Cancer UK is a voluntary organisation based in London. It is a registered charity in England and Wales (1005541) and in Scotland (SC039332). Registered company number 02653887.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	The organisation has not received funding from any of the relevant companies in the last 12 months.
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 carers to include in your submission?	Desk research and our own knowledge of the experiences of men. Further evidence from people contacting our specialist nurse service or emailing our support services.

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?	A diagnosis of metastatic prostate cancer typically causes fear, distress and anxiety for patients and their families, as the incurable nature of advanced disease can be very difficult to manage psychologically. One of the primary ways in which advanced prostate cancer affects the lives of patients is through the symptoms it can cause, although these vary between individuals. It is not possible to be specific about the symptoms for newly diagnosed high-risk hormone-sensitive metastatic prostate cancer, as there is limited evidence available that is specific to this sub-population of men. Therefore here, we discuss evidence-based symptoms for advanced prostate cancer. One of the most common symptoms is fatigue, which can affect a man's ability to carry out every day self-care tasks and social activities, as well as impacting his concentration, sleep, memory and decision-making. Cancer-related fatigue affects up to 90% of advanced prostate cancer patients and is often referred to as the most distressing side effect.[1] Bone is the most common site of metastases, and often results in bone pain, affecting 75% of symptomatic patients with metastatic prostate cancer.[2] Bone pain can have a significant impact on a man's quality of life, making simple things such as sleeping, walking, and other movement painful. If metastatic prostate cancer has spread to the bladder or urethra, or the cancer presses on the urethra, it can cause urinary issues, including incontinence, urine retention, blood in the urine and kidney problems. There are also side effects which are less common but can equally impact a man's life day-to-day, such as bowel problems, anaemia, symptoms caused by high levels of calcium in the blood and loss of appetite. The symptoms of metastatic prostate cancer and the side effects of treatments can make it difficult for men with the disease to work. A diagnosis of advanced prostate cancer can also significantly impact a man's mental health. The emotional burden of the diagnosis is often huge, particularly as there are no curative treatments for disease at this stage and can result in men experiencing anxiety and/or depression, which can also be exacerbated by fatigue. It is also often emotionally difficult for loved ones of men with advanced prostate cancer and can put strain on relationships. Advanced prostate cancer and its treatments might mean that partners or family need to do more for patients, such as running the home or taking on caring responsibilities, and might affect the ability of a partner providing care to work.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Men with newly diagnosed metastatic prostate cancer do not have curative treatment options available to them. They (and their carers) will weigh up the quantity of life granted by any treatment with the quality of life during that period including any side-effects or consequences of treatment. Common treatments for men in this indication include androgen deprivation therapy (ADT) alone, or a combination of ADT and chemotherapy (docetaxel). Data from the STAMPEDE trial and CHAARTED study has shown that the addition of docetaxel to ADT provides longer survival for men at this stage of the disease.[3,4] ADT alone can cause a range of adverse effects, including hot flushes, fatigue, sexual dysfunction, and strength and muscle loss. Additionally, hormone therapy is associated with the side effect of bone weakening and fracture.[5] Additional effects from the combination treatment (docetaxel and ADT) include febrile neutropenia (6% of patients), effects on sensory nerves (1%) and effects on motor nerves (1%). The addition of darolutamide to docetaxel and ADT (triplet therapy) provides further survival benefits beyond those of ADT alone or ADT with docetaxel. While the combination of docetaxel and ADT or darolutamide triplet therapy are more effective than ADT alone, many men are contraindicated for chemotherapy, too physically unfit to tolerate it, or would prefer to avoid it. This is illustrated by reports of low levels of uptake of triplet therapy, with inequalities also cited in uptake of docetaxel by ethnicity and men with more comorbidities.[6] Additionally, in practice, ADT monotherapy use remains high in Europe,[7] and we have received similar anecdotal evidence from our Specialist Nurses of patients receiving ADT monotherapy. This may suggest that further treatment options with improved effectiveness are needed. Other alternative treatments that don't require chemotherapy include the other androgen receptor pathway inhibitors apalutamide and enzalutamide, which are added to ADT, and show comparable or improved effectiveness to the combination of docetaxel and ADT.[8] These treatments provide additional options to men who are unsuitable for or prefer to avoid chemotherapy. Direct comparisons between these inhibitors (also known as Novel Hormone Therapies or NHTs) are not available from any individual trial, but meta-analysis has demonstrated that the efficacy of these inhibitors, in terms of increasing chance of overall survival, are comparable. These NHTs bring their own profiles of adverse effects, including fatigue, hot flushes and hypertension. Although several treatments are available for men in this indication, as described above, we have heard directly from men that there is a need for more treatments for advanced prostate cancer.

8. Is there an unmet need for patients with this condition?	Existing NHTs give substantial benefits for patient survival over ADT alone and have provided an effective alternative for patients who are contraindicated to or prefer to avoid chemotherapy. However, they bring their own risks of adverse effects, which can severely impact a patient's life day-to-day. Therefore, increasing the number of effective treatments is critical for patient choice, giving them the option to avoid specific side effects. Some patients may already have a restricted pool of these treatments available to them due to existing comorbidities, and there are small subpopulations who may be unsuitable for existing NHTs (e.g. patients suffering from seizures or with an increased seizure risk are unlikely to be suitable for either enzalutamide or apalutamide), so further treatment options are needed. Prior to the interim policy that made this treatment available in England,[9] we were contacted by several patients in this indication who either could benefit from abiraterone but weren't able to access it or were paying to receive it privately and had concerns about affordability, highlighting that patients want this treatment to be made available.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Abiraterone treatment provides a significant improvement in overall patient survival compared to hormone therapy alone. Along with other androgen receptor pathway inhibitors (apalutamide and enzalutamide), abiraterone provides an overall survival benefit (38% lower risk of death) compared to hormone therapy alone with little to no decrease in quality of life.[10] Use of abiraterone led to no worse outcomes in reported fatigue or musculoskeletal events when compared to placebo and ADT comparator arms in the LATITUDE trial.[11] Abiraterone also has comparable effectiveness but leads to better quality of life than docetaxel chemotherapy,[8] and is similarly effective to enzalutamide and apalutamide. This treatment therefore provides another effective option for patients who are unsuitable for or wish to avoid chemotherapy and would represent an additional choice for all patients at this stage of the disease, providing a greater sense of control which can help ease anxiety. This treatment would also benefit patients who have comorbidities or take other medication that impacts treatment selection, and if approved, it may be the only treatment option available to them that provides survival benefits over ADT alone. For example, those with kidney or liver problems, brain injuries or cancer, or a history of strokes may not be suitable for treatment with apalutamide, while enzalutamide may not be suitable for patients with a history of falls, fatigue, or memory/concentration issues. Patients suffering from seizures or with an increased seizure risk are unlikely to be suitable for either enzalutamide or apalutamide but may be eligible for abiraterone. Abiraterone also has a different profile of side effects to existing treatments, so making it available increases patient control over how treatment might affect their lives.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Abiraterone treatment carries the risk of side effects, our understanding of which is mostly from patients with metastatic disease generally. The most common side effects of this treatment are fluid retention, hypokalaemia, liver problems, high blood pressure, urinary tract infections and diarrhoea. In a clinical trial, a cohort of 1,008 men with metastatic castration-resistant prostate cancer (mCRPC) without previous chemotherapy were assigned to receive either abiraterone acetate plus prednisolone or placebo plus prednisolone. The abiraterone treatment resulted in men developing fluid retention (28%), hypokalaemia (17%), and hypertension (22%). 33% of patients had a serious adverse effect.[12] Abiraterone is also taken alongside steroids (commonly prednisolone), which bring their own risk of side effects, such as indigestion, water retention and a higher likelihood of infections. However, this is not unique to abiraterone, as all treatments for advanced prostate cancer can cause side effects. In a study with a median follow up of 40 months, grade 3 to 5 adverse events were reported in 47% of patients taking abiraterone with hormone therapy, 52% of patients receiving docetaxel with hormone therapy, and 33% of patients taking hormone therapy alone.[13] In the same study, a higher incidence of hepatic disorder and hypertension was also reported for abiraterone treatment compared to ADT alone. However, hepatic disorders can be mild and temporary,[14] and there were no differences in a number of other adverse events including hot flashes. For comparison, the ENZAMET trial showed that enzalutamide (another androgen receptor inhibitor) and ADT had 14% more grade 3 adverse events than standard care in patients with mHSPC.[15] Trial data has shown that patient quality of life is higher for abiraterone than for docetaxel, but the treatment course tends to be much longer (until disease progression versus six 3-weekly cycles respectively). Use of abiraterone as a treatment for mHSPC also removes it as an option if the cancer later becomes hormone resistant. The most efficacious treatment sequence also remains unclear, including in the mCRPC setting.[16] However, these issues can be taken into account when making treatment decisions and may be mitigated by availability of other late-stage treatments.

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.	This combination would expand the treatment options for patients who are unsuitable for chemotherapy or would prefer to avoid it. Some patients may already have restricted options in terms of approved NHTs available to them due to existing comorbidities, and there are likely to be patients who are unsuitable for existing NHTs. Additionally, while enzalutamide and apalutamide have very similar profiles of drug-drug interactions, abiraterone has a less similar profile, potentially making it a good option for patients taking other medications.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Prostate cancer is a condition that can only affect people with a prostate, and therefore men and others assigned male at birth. Recent work has highlighted that only 39.0% of mHSPC patients in England receive treatment intensification despite level 1 evidence and NICE recommendation. Moreover, inequalities were reported in NHT uptake in this indication across practices in England, for older men, Black men, and men in deprived areas.[6] This underuse of treatment intensification is likely to also represent an issue for this treatment. An additional equity consideration is that this treatment would increase choice for patients with currently unmet needs, including those with comorbidities.

Other issues

13. Are there any other issues that you would like the committee to consider?	Since the expiry of its patent in 2022, abiraterone is now very cheap, with NHS trusts in England paying an average of £77 for a 28-day supply based on 2024 data,[17] compared to thousands of pounds while under patent. Analysis of STAMPEDE trial data further showed that use of abiraterone as a treatment for metastatic prostate cancer would be cost saving to the NHS, highlighting the likely financial benefit of its approval across the UK.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• The impact metastatic prostate cancer can have on a patient's life is huge – both in terms of symptoms and the burden of the diagnosis itself. • It is therefore imperative that patients have a greater treatment choice in this indication, giving them some control over how treatment will affect their lives day-to-day. • Abiraterone with prednisolone and ADT represents an effective treatment option that would particularly benefit those unsuitable for current treatment options (including other NHTs and chemotherapy). • This treatment combination represents an effective option (in terms of survival and progression) that is comparable to other NHTs, but with the added benefit of low-cost generic versions being available.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

References

1. Cornford, P., Robijn, E., Rogers, E., Wassersug, R. & Fleure, L. Fatigue in Prostate Cancer: A Roundtable Discussion and Thematic Literature Review. *Eur. Urol. Open Sci.* 63, 119–125 (2024).
2. Drudge-Coates, L. *et al.* Recognizing Symptom Burden in Advanced Prostate Cancer: A Global Patient and Caregiver Survey. *Clin. Genitourin. Cancer* 16, e411–e419 (2018).
3. Sweeney, C. J. *et al.* Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. *N. Engl. J. Med.* 373, 737–746 (2015).
4. James, N. D. *et al.* Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet Lond. Engl.* 387, 1163–1177 (2016).
5. Bone problems and osteoporosis in prostate cancer. https://www.cancerresearchuk.org/about-cancer/prostate-cancer/practical-emotional-support/hormone-symptoms/sex-hormones-bone-loss-men.
6. Dodkins, J. *et al.* Does Research from Clinical Trials in Metastatic Hormone-sensitive Prostate Cancer Treatment Translate into Access to Treatments for Patients in the "Real World"? A Systematic Review. *Eur. Urol. Oncol.* 7, 14–24 (2024).
7. Raval, A. D., Chen, S., Littleton, N., Constantinovici, N. & Goebell, P. J. Underutilization of androgen deprivation therapy (ADT) intensification for the treatment of men with metastatic hormone-sensitive prostate cancer (mHSPC): A systematic review of real-world database studies. *J. Clin. Oncol.* 42, 66–66 (2024).
8. Wang, L. *et al.* Comparison of Systemic Treatments for Metastatic Castration-Sensitive Prostate Cancer. *JAMA Oncol.* 7, 412–420 (2021).
9. NHS England, . Abiraterone acetate and prednisolone for high-risk, hormone-sensitive metastatic prostate cancer (adults) [2424]. https://www.england.nhs.uk/publication/abiraterone-acetate-and-prednisolone-for-high-risk-hormone-sensitive-metastatic-prostate-cancer-adults-2424/ (2024).
10. Fizazi, K. *et al.* Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. *N. Engl. J. Med.* 377, 352–360 (2017).
11. Fizazi, K. *et al.* Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. *Lancet Oncol.* 20, 686–700 (2019).
12. Ryan, C. J. *et al.* Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy. *N. Engl. J. Med.* 368, 138–148 (2013).
13. James, N. D. *et al.* Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. *N. Engl. J. Med.* 377, 338–351 (2017).
14. Colomba, E. *et al.* Liver tests increase on abiraterone acetate in men with metastatic prostate cancer: Natural history, management and outcome. *Eur. J. Cancer* 129, 117–122 (2020).
15. Davis, I. D. *et al.* Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. *N. Engl. J. Med.* 381, 121–131 (2019).
16. Cassinello, J. *et al.* Optimal treatment sequencing of abiraterone acetate plus prednisone and enzalutamide in patients with castration-resistant metastatic prostate cancer: A systematic review and meta-analysis. *Cancer Treat. Rev.* 93, (2021).
17. Drugs and pharmaceutical electronic market information tool (eMIT). *GOV.UK* https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit (2024).

NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Abiraterone (originator and generics) for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer (review of TA721) [ID6378]

Patient Organisation Submission

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	[redacted]
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 around 120 support groups in England and Wales and through them have several thousand individual members - men and their families whose lives have been affected by prostate cancer. We receive funding from a wide variety of sources including The National Lottery Fund, Movember, Charitable Trusts, Income from individual donations and fund raising events, Prostate Cancer UK, Corporate donations, and income from the pharma industry as either project based grants, payment for services provided by members or unrestricted grants. During tax year 24/ 25 total pharma income contributed 8% of our total income
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12	**YES** Bayer £5,000 Grant Financial support for Annual Conference £13,800 Grant towards project 'Many Faces' campaign highlighting shared experience of patients

months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Ipsen: £4,850 Grant towards project 'Many Faces' campaign highlighting shared experience of patients Johnson & Johnson (Janssen Cilag): £10,000 Financial support for Annual Conference
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 carers to include in your submission?	Gathering regular input from our members is a priority, and we achieve this through various channels such as at local and national meetings held online as well as in person. Sharing personal experiences of living with PCa is a fundamental function of Tackle. Additionally, we engage in direct communication with individuals and address questions and concerns raised by patients when appropriate. Many of our local groups host local helplines from which we can obtain feedback when required. Our medical advisory board is in place to offer guidance whenever necessary. Combinations of Androgen Deprivation Therapy (ADT) with Novel Hormonal Agents (NHAs) are already widely utilized and endorsed by NICE. This cost comparison appraisal serves as a natural extension of these established treatments. Many patients undergoing diagnosis and treatment find themselves managing both hormone-sensitive and metastatic prostate cancer. The complexities of treatment, including efficacy and side effects, are frequently discussed within support groups and helplines. Conversations among patients reflect not just concerns about therapeutic outcomes but also the broader impact on their well-being. Having engaged with many of these individuals over the years, I have developed a strong understanding of their needs. With the backing of Tackle Prostate Cancer, I feel it is appropriate for me to advocate 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?	Hormone sensitive metastatic prostate cancer (hsmPca) may develop as a progression from the non-metastatic phase but can also occur in newly diagnosed men. A man newly diagnosed with metastatic hormone sensitive metastatic prostate cancer 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. 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 need to make plans accordingly. The possibility of extending life and increasing the time before further progression of the disease and the onset of considerable extra problems such as pain from metastases is of paramount importance. Quality of life is a crucial consideration for patients at any stage of their disease. The journey of prostate cancer treatment involves substantial emotional and physical impact for not only patients, but also family members and caregivers. The advantages of 'Doublet' or 'Dual' combination therapy of ADT & NAHs or Chemotherapy have undoubtedly had a great positive influence on all of those people whose lives have been affected by prostate cancer.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Historically, hormone-sensitive metastatic prostate cancer (hsmPca) was treated with monotherapy using Androgen Deprivation Therapy (ADT) alone. However, findings from the Stampede trials demonstrated significant benefits of combining ADT with chemotherapy, leading to a rapid shift in the standard of care. Today, this combination is considered the established treatment approach, and ADT alone is no longer recommended unless there are good reasons to the contrary. Despite strong evidence supporting combination therapies, recent data from the National Prostate Cancer Audit indicate that their adoption remains suboptimal, with approximately 30% of patients potentially receiving inadequate treatment. For those who are either unable or unwilling to undergo chemotherapy, or who experience severe early side effects, novel hormonal agents (NHAs) have been approved by NICE as an alternative therapeutic option. A wide choice of NHAs for both clinicians and patients is now available but generic versions of established drugs can be considerably less costly to the NHS than newer drugs.
8. Is there an unmet need for patients with this condition?	Yes. Whilst most patients will be suitable for similar combination therapies there will be some who are, for various reasons, unable to take some or any of those currently available. Generic versions of established drugs are now available. Approval for use of Abiraterone in hsmPCa may result in cost savings to NHS and increased choice of drugs to both clinicians and patients.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The efficacy of Abiraterone was established in a previous unsuccessful NICE Committee appraisal – ID945. Despite an appeals process, a decision not to recommend Abiraterone was made. Costs of the drug to the NHS may have been a significant factor. Now that the drug is available generically, and thus at a lower cost to the NHS, it is logical that this situation should be re-examined through this cost comparison appraisal.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	If a treatment is effective and suitable then patients will accept side effects as long as they are not severe. Dosage regime should be easy and acceptable. Drug treatment does not require regular visits to hospital and most monitoring can be achieved in the community.

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.	Apart Scotland, use of Abiraterone in mhsPCa is not currently approved in newly diagnosed high-risk hormone-sensitive prostate cancer. A positive decision here would make this drug universally available within the UK. This would seem a logical step forward.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	N/A

Other issues

13. Are there any other issues that you would like the committee to consider?	There are some patients who, for various reasons, were commenced on abiraterone in preference to either docetaxel or enzalutamide for their newly diagnosed high risk metastatic hormone sensitive PCa . Some will have been pre-Covid which accelerated the approval by NICE of the substitution of NHAs for chemotherapy. These patients may well have been previously on a trial or having their drugs costs supported by private medical insurance. They could be regarded as having 'fallen foul' of the NICE decision to approve enzalutamide and not abiraterone in this clinical scenario. Some are having now to fund their treatment on a 'self-pay' basis. This is likely to be a very small number of patients and the overall increase in cost to the NHS will be comparatively very small. However, it would bring this group of patients in line with those being prescribed enzalutamide on the NHS. Whether this is truly and consideration under 'Equality Issues' is not clear.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Current standard of care of newly diagnosed high-risk hormone sensitive metastatic prostate cancer is combination therapy and not monotherapy unless there are specific reasons to the contrary:
	  o ADT with chemotherapy
	  o ADT with a Novel Hormonal Agent
	• Abiraterone has been shown to be effective as a NAH when used in this context
	• Abiraterone is well tolerated by patients. Abiraterone is comparable to those NAHs in current usage.
	• Now that Abiraterone is available as a generic drug, it would seem logical to allow it to be added to the choice of NAHs available to clinicians when treating patients with newly diagnosed high-risk metastatic hormone sensitive prostate cancer
	• Cost savings to the NHS may be possible

Thank you for your time.

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Adapted Cost-comparison Evaluation

Abiraterone (originator and generics) for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer (review of TA721) [ID6378]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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. 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.

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. 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.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Monday 25 August.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, 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 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.

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Part 1: Treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancerand current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Prof Alison Birtle
2. Name of organisation	Working at Lancashire Teaching Hospitals
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 newly diagnosed high-risk hormone-sensitive metastatic prostate cancer? ☐ A specialist in the clinical evidence base for newly diagnosed high-risk hormone-sensitive metastatic prostate cancer 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 nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
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 Please note that I have been asked by NICE themselves to complete this as a clinical expert and am not directly representing a medical professional organisation.I have not seen current documentation other than the forms sent to me and so am commenting directly on the technology
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.

8. What is the main aim of treatment for newly diagnosed high-risk hormone-sensitive metastatic prostate cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To improve local symptoms, prevent or delay complications of progression, and to improve both overall survival and time to progression and development of castrate resistant metastatic disease, all of which cause incur additional health care costs
9. What do you consider a clinically significant treatment 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 newly diagnosed high-risk hormone-sensitive metastatic prostate cancer?	Yes In patient unable to receive apalutamide or enzalutamide, this is an option compared with ADT alone and would improve 5 year overall survival from 55 to 72% in newly diagnosed low risk metastatic hormone sensitive prostate cancer. It is well tolerated with no current unexpected side effects identified compared to other indication for abiraterone.
11. How is newly diagnosed high-risk hormone-sensitive metastatic prostate cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care?	NCCD EAU and ESMO guidelines state that all patients with adequate performance status and life expectancy from other comorbidities should receive with doublet with an androgen receptor pathway inhibitor (ARPi) such as enzalutamide, apaluatamide, abiraterone in addition to ADT, or triplet (ADT, Arpi and docetaxel chemotherapy) for low risk/low volume patients they also receive radiotherapy to the prostate. In England we use either doublet or triplet for these patients + prostate radiotherapy . The pathway should be well designed. However the national prostate caner audit confirms that we are undertreating significant numbers of newly diagnosed men with hormone sensitive metastatic prostate cancer. This would add an additional option for patients especially those unsuitable for doublet with ADT/Enza or ADT/Apa or triplet (ADT/dara/Docetaxel chemotherapy)
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Secondary care speciality uro oncology clinics. The UK uro oncology community are already using abiraterone in other indications and are well versed in prescribing and toxicity management and monitoring. It would need some

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	additional monitoring for patient but this could be telephone follow up. Most patient do have home blood pressure monitoring
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	In patient unable to receive apalutamide or enzalutamide, this is an option compared with ADT alone and would improve 5 year overall survival from 55 to 72% in newly diagnosed low risk metastatic hormone sensitive prostate cancer. It is well tolerated with no current unexpected side effects identified compared to other indication for abiraterone.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Poor performance status patients (only selected PS 2 patients unless the PS is due to the cancer and not other comorbidities), patients with contraindications to steroids or significant pre existing liver dysfunction or hypertension poorly controlled
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 treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Practical implications are additional monitoring for patients- usually SPC recommends 2 weekly Blood pressure and liver function tests for first 12 weeks of treatment and then monthly. These need either robust collaboration between primary and secondary care or sufficient staffing to monitor patients via the oncology teams. There are also concomitant prednisolone and a protein pump inhibitor required with abiraterone.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing . require staging and confirmation of diagnosis and suitability before starting and discontinuation due to either toxicity or progression.
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? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	If complications of castrate resistant disease are reduced or delayed due to a more effective first line treatment then this will mean fewer life affecting complications such as symptomatic skeletal events (spinal cord compression/pathological fractures)
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 improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Unmet need- some patients may currently not receive alternative androgen pathway inhibitors due to eg risk of epilepsy, or significant skin conditions (considering other ARPi in this indication) and thus this would offer an alternative for those patients who would otherwise received ADT alone. For patients where there is potential risk of significant worsening of eg cognitive function with other ARPi in this space, this would provide an alternative.
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?	Side effects are in line with other indications for this drug and are well recognised and managed.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials?	We have not been allowed to use abi for this indication- however it has robust survival data and good quality of life as documented above

• 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?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	There are 6 systematic reviews and network Meta analyses including Latitutde, CHAARTED and stampede trials in the NMA's The post hoc sub study by James et al may not have been previously included and the five year follow u[data from stampede may not have been included previously
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA712 and TA741?	See above
23. How do data on real-world experience compare with the trial data?	Favourably, no additional toxicity concerns and efficacy similar in patients consistent with real life practice.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? 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. Please state if you think this evaluation could	As above, some patients may currently not be suitable for the approved options and there is thus an unmet need. This may also allow biologically fit older patients to be offered more than ADT alone and to improve the numbers of patient treated .

• exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

There is a current unmet need for an additional option for patients unsuitable for the currently approved androgen receptor pathway inhibitors for metastatic hormone sensitive prostate cancer

There is robust patient support for this

There are no differences in published toxicity for abiraterone in other licensed indications

Quality of life is improved for patients and progression delayed.

Click or tap here to enter text.

Thank you for your time.

Your privacy

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Adapted Cost-comparison Evaluation

Abiraterone (originator and generics) for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer (review of TA721) [ID6378]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

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

Information on completing this form

In part 1 we are asking you about living with newly diagnosed high-risk hormone-sensitive metastatic prostate cancernewly diagnosed high-risk hormone-sensitive metastatic prostate cancer. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

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.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Friday 15 August.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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Patient expert statement

Part 1: Living with this condition or caring for a patient with newly diagnosed high-risk hormone-sensitive metastatic prostate cancer

Table 1 About you, newly diagnosed high-risk hormone-sensitive metastatic prostate cancer, current treatments and equality

1. Your name	Ellie Blake
2. Are you (please tick all that apply)	☐ A patient with newly diagnosed high-risk hormone-sensitive metastatic prostate cancer? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with newly diagnosed high-risk hormone-sensitive metastatic 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 and provide answers when 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

Patient expert statement

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 or experience (for example, 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
6. What is your experience of living with newly diagnosed high-risk hormone-sensitive metastatic prostate cancer? **If you are a carer for someone with newly diagnosed high-risk hormone-sensitive metastatic prostate cancer, please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for newly diagnosed high-risk hormone-sensitive metastatic prostate cancer on the NHS? **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 newly diagnosed high-risk hormone-sensitive metastatic prostate cancer (for	

example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of abiraterone over current treatments on the NHS please describe these. For example, the effect on your quality of life, your 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 abiraterone help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of abiraterone over current treatments on the NHS please describe these. For example, are there any risks with abiraterone? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from abiraterone 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	
12. Are there any potential equality issues that should be taken into account when considering newly diagnosed high-risk hormone-sensitive metastatic	

prostate cancer and abiraterone? Please explain if you think any groups of people with this condition are particularly disadvantage 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 Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
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Adapted Cost-comparison Evaluation

Abiraterone (originator and generics) for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer (review of TA721) [ID6378]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

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

Information on completing this form

In part 1 we are asking you about living with newly diagnosed high-risk hormone-sensitive metastatic prostate cancernewly diagnosed high-risk hormone-sensitive metastatic prostate cancer. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

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.

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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. Please type information directly into the form.

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. 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.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Friday 15 August.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, 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 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.

Patient expert statement

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with newly diagnosed high-risk hormone-sensitive metastatic prostate cancer

Table 1 About you, newly diagnosed high-risk hormone-sensitive metastatic prostate cancer, current treatments and equality

1. Your name	Stephen Allen
2. Are you (please tick all that apply)	☐ A patient with newly diagnosed high-risk hormone-sensitive metastatic prostate cancer? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with newly diagnosed high-risk hormone-sensitive metastatic 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 and provide answers when 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

Patient expert statement

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 or experience (for example, 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
6. What is your experience of living with newly diagnosed high-risk hormone-sensitive metastatic prostate cancer? **If you are a carer for someone with newly diagnosed high-risk hormone-sensitive metastatic prostate cancer, please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for newly diagnosed high-risk hormone-sensitive metastatic prostate cancer on the NHS? **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 newly diagnosed high-risk hormone-sensitive metastatic prostate cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these	

9a. If there are advantages of abiraterone over current treatments on the NHS please describe these. For example, the effect on your quality of life, your 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 abiraterone help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
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11. Are there any groups of patients who might benefit more from abiraterone 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	
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13. Are there any other issues that you would like the committee to consider?	I was responsible for completing and submitting the Patient Organisation Statement on behalf of Tackle Prostate Cancer. I have nothing further to add to that statement

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
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Abiraterone (originator and generics) for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer (review of TA721) [ID6378]

EAG assessment report

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School
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Author contributions

Alex Allen	Clinical evidence lead and project manager. Led on the systematic literature review and drafted sections of the report.
Jamie Bowater	Statistician and clinical evidence reviewer. Drafted sections of the report.
Saul Stevens	Health economist with responsibilities for the assessment of economic evidence and the development of the economic analysis. Drafted sections of the report.
Alan Lovell	Information Specialist responsible for developing and conducting evidence searches. Drafted sections of the report.
Dr Matthew Fittall	Expert clinical advice to the EAG about metastatic hormone-sensitive prostate cancer and its treatment
Dr Andrew Hudson	Expert clinical advice to the EAG about metastatic hormone-sensitive prostate cancer and its treatment
Dawn Lee	Project director, economic evidence lead, and guarantor of the EAG assessment. Drafted sections of the report.

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Confidential information

Confidential information contained within this report is shown in Table 1.

Table 1: Confidential information in this report

Brief description	Status	Page number(s)	Source
QALY outcome information from previous TAs	CON	72 to 74	Document B TA712 Document B TA721 Document B TA741 Document B TA903
RDI information from previous TAs	CON	82	Document B TA712 Document B TA721 Document B TA741 Document B TA903
Baseline characteristics of mHSPC participants in TITAN	CON	134	Document B TA741

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Abbreviations

Term	Definition
Abi	Abiraterone and prednisolone
ADT	Androgen deprivation therapy
AE	Adverse event
ALT	Alanine Aminotransferase
Apa	Apalutamide
AR	Androgen receptor
ARPI	Androgen Receptor Pathway Inhibitor
ASCO	American Society of Clinical Oncology
BNF	British National Formulary
CI	Confidence interval
CRPC	castrate resistant prostate cancer
DHSC	Department of Health and Social Care
DHT	Dihydrotestosterone
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
eMIT	Drugs and pharmaceutical electronic market information tool
Enz	Enzalutamide
FU	Follow-up
GS	Gleason score
IQR	Interquartile range
MAUDE	Manufacturer and User Facility Device Experience
MHRA	Medicines & Healthcare products Regulatory Agency
HealthTech	Health Technologies Evaluation Programme
HR	Hazard ratio
LHRH	Luteinizing Hormone-Releasing Hormone
MCDA	Multi-criteria decision analysis
mCRPC	metastatic castrate resistant prostate cancer
mCSPC	metastatic castration sensitive prostate cancer
mHRPC	metastatic hormone relapsed prostate cancer
mHSPC	metastatic hormone sensitive prostate cancer
mnths	months
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

Term	Definition
NICE CG	NICE clinical guideline
NICE HTE	NICE health technology evaluation
NICE QS	NICE quality standard
NMA	Network meta-analysis
OLE	Open-label extension
OS	Overall survival
PFS	Progression-free survival
PSSRU	Personal Social Services Research Unit
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality adjusted life year
QoL	Quality of life
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomised controlled trial
RDI	Relative dose intensity
rPFS	radiographic progression-free survival
SC	Some concerns
SD	Standard deviation
SmPC	Summary of product characteristics
TA	Technology Appraisal
VAS	Visual analogue scale

Executive Summary

Background

In TA721, abiraterone (and prednisone with androgen deprivation therapy), was appraised for treatment of newly diagnosed people with high-risk hormone-sensitive metastatic prostate cancer (mHSPC). While it was found to be effective and safe for treating adults with high-risk mHSPC, it was not recommended as it was found not to be cost-effective in comparison to ADT alone and docetaxel with ADT, even accounting for a proposed commercial arrangement. However, abiraterone has become available as a generic at a substantially reduced price. Therefore, NICE decided to review the decision made in TA721 as a cost-comparison versus the relevant comparators in the NHS treatment pathway.

Clinical and technological evidence

A cost comparison case can be made if a health technology is likely to provide similar or greater health benefits than technologies recommended in published NICE technology appraisal guidance for the same indication at a similar or lower cost. The aim of the clinical review was to assess whether abiraterone does provide similar or greater health benefits versus apalutamide with ADT and enzalutamide with ADT. A network meta-analysis (NMA) was conducted using four RCTs that linked the treatments via a common comparator, ADT alone. Only one RCT (LATITUDE) recruited the relevant population, people with high-risk mHSPC. Where possible, subgroup analysis from the other RCTs was used to better reflect this population. Three of the trials had open-label extension (OLEs) appended to the end of the randomised period whereby people in the comparator arm were permitted to use the intervention until the end of the trial. These OLEs led to deviations from the intended interventions in three trials and the proportions deviating was not consistent. In response to this, NMAs were conducted using data from each trial prior to the OLE occurring and at the latest timepoint available for each trial (after crossover had been permitted). In the ARCHES trial (enzalutamide), the OLE started so early (after a median of 14.4 months on randomised treatment) that the radiographic progression-free survival (rPFS) and overall survival (OS) data were highly immature and uncertain prior to the OLE.

The NMAs consistently found abiraterone provided similar or greater health benefits in terms of OS in the analysis prior to the OLE and after the OLE as judged using benchmarking from the ASCO guidelines[1]. Two notes of caution, the 95% credible intervals were often wide offering a wide range of potential true effects and the point estimates at the longer timepoints offered a

very small benefit for the comparators. Secondly, in the OS NMA at the later timepoint there had been a higher proportion crossing from comparator treatment to intervention treatment in the enzalutamide trial and the apalutamide trial and this biased the results in favour of abiraterone. However, the EAG were reassured by the lack of meaningful or significant difference between treatments across both analyses and therefore concluded that assuming a similar level of health benefits was reasonable.

These analyses were primarily in people with high-risk mHSPC. The NMA for rPFS was only possible prior to the OLEs and found abiraterone to be similarly effective to apalutamide. The result versus enzalutamide (ARCHES) used highly immature data and was consequently too uncertain to draw any conclusions on the similarity or dissimilarity of effect. However, recent research in Shore et al. (2025) analysed 31 RCTs in people with mHSPC (including ARCHES, LATITUDE, STAMPEDE, and TITAN) and found rPFS was a reliable surrogate for OS.[2] Therefore, given the strong evidence of similarity of effect between enzalutamide and abiraterone in OS, it is rational to assume a similarity of effect for rPFS given the absence of strong clinical evidence in either direction.

The smaller NMA on health-related quality of life (HRQoL) found no difference between abiraterone and enzalutamide. The safety analyses used the full trial populations, high-risk mHSPC from LATITUDE and mHSPC for ARCHES, STAMPEDE, and TITAN. The NMAs found people on abiraterone had statistically significantly more Grade 3 and above adverse events, than apalutamide or enzalutamide. However, in the EAG's clinical expert's experience of using abiraterone in their practice, adverse events were treatable and did not commonly lead to treatment discontinuation.

In sum, the NMAs consistently found abiraterone provided similar or greater health benefits in terms of OS versus both comparators and for rPFS versus apalutamide. The NMAs did find treatment with abiraterone to result in a higher adverse events burden than enzalutamide or apalutamide.

Economic evidence

The economic analysis compared the costs of abiraterone, enzalutamide and apalutamide from the perspective of the NHS over a three-year time horizon. In the base case, abiraterone was associated with lower costs than both enzalutamide and apalutamide, driven primarily by differences in acquisition costs. The difference in incremental costs considering the treatments

at list price was -£102,973 for abiraterone vs enzalutamide and -£103,012 for abiraterone vs apalutamide. Probabilistic sensitivity analysis indicated that abiraterone remained the least costly option in all simulations. Deterministic sensitivity and scenario analysis showed that the results were most insensitive to the majority of model parameters with the only the time horizon (equal to the mean time on treatment) showing any real sensitivity.

When considering treatments at list price the QALY gains required for abiraterone to no longer be cost-effective if abiraterone were in fact less effective than comparators were considerably larger than the range considered plausible based upon previous economic analyses.

Economic analyses including confidential discounts are presented in the cPAS appendix.

Key points for decision makers

1. Three of the four trials in the NMA recruited a wider population than the relevant high-risk mHSPC but relevant subgroup analysis was available for the key OS and rPFS outcomes.
2. Three of the four trials in the NMA included an OLE where people in the comparator arm were permitted to crossover to the intervention and led to large deviations from the intended interventions at later timepoints. Where possible, two NMAs, one before crossover was permitted and one after crossover was permitted, were conducted for each outcome.
3. The NMAs consistently found abiraterone provided similar or greater health benefits in terms of OS versus both comparators and similar health benefits in rPFS versus apalutamide. Given the research published by Shore et al. (2025)[2] and the evidence of similarity of effect between enzalutamide and abiraterone in OS, it was rational to assume a similarity of effect for rPFS given the absence of strong robust clinical evidence in either direction.
4. The NMAs found people on abiraterone had statistically significantly more Grade 3 and above adverse events, including hypertension, than apalutamide or enzalutamide. The EAG's expert advice was that they were treatable and did not commonly lead to treatment discontinuation.
5. In the EAG's base case, abiraterone was associated with lower costs than both enzalutamide and apalutamide, driven primarily by differences in acquisition costs. The difference in incremental costs considering the treatments at list price was -£102,973 for abiraterone vs enzalutamide and -£103,012 for abiraterone vs apalutamide.

6. When considering treatments at list price the QALY gains required for abiraterone to no longer be cost-effective if abiraterone were less effective than comparators were considerably larger than the range considered plausible based upon previous economic analyses.

1. INTRODUCTION AND BACKGROUND

1.1. Introduction

Abiraterone acetate (ZYTIGA®), henceforth called abiraterone, is an androgen receptor pathway inhibitor (ARPI). Other ARPIs relevant to this appraisal were apalutamide, enzalutamide, and darolutamide. However, apalutamide, enzalutamide, and darolutamide are *androgen receptor antagonists*, while abiraterone is an *androgen synthesis inhibitor*. Androgen receptor antagonists work by blocking the effects of androgens, male sex hormones, by preventing them from binding to androgen receptors, which are found in prostate cells and other tissues. On the other hand, androgen synthesis inhibitors, such as abiraterone, inhibit the production of androgens, thus depriving cancer cells of the necessary fuel for growth.

In TA721, abiraterone (with prednisone and androgen deprivation therapy, hereafter ADT), was appraised for treatment of newly diagnosed people with high-risk hormone-sensitive metastatic prostate cancer (high-risk mHSPC). It was compared to ADT alone and docetaxel with ADT and not to other ARPIs. While it was found to be effective and safe for treating adults with high-risk mHSPC, it was not recommended as it was found not to be cost-effective in comparison to ADT alone and docetaxel with ADT, even accounting for a proposed commercial arrangement.

Since TA721 other ARPIs, in combination with ADT, have received recommendations and abiraterone has become available as a generic at a substantially reduced price. Therefore, NICE decided to review the decision made in TA721. The EAG's clinical experts did note that abiraterone with ADT was already commissioned by NHS England (NHSE) at the time of writing for this report. However, NICE explained that a formal recommendation would facilitate greater access across the NHS and inform future commissioning policy.

1.2. Underlying health problem

1.2.1. Prostate cancer

Prostate cancer was the most common and most frequently diagnosed form of cancer in men in the UK in 2020.[3] There were approximately 55,100 new prostate cancer cases annually in the UK, of which 13% presented with metastatic disease at diagnosis (data from 2017-2019).[4] A recent review found that in the UK, the number of new prostate cancer cases increased from 109 to 159 per 100,000 person-years between 2000 and 2021.[5] Between 2017-2019, there were approximately 12,000 prostate cancer deaths in the UK each year.[5]

1.2.2. Demographic risk factors

Prostate cancer risk increases significantly with age, affecting about 1 in 6 men overall.[6] However, it disproportionately impacts people with Black (Black African, Black Caribbean, and Other Black) ethnicity, with around 1 in 4 diagnosed in their lifetime.[7] Clinical experts informed the EAG that people with Black ethnicity are twice as likely than people with White ethnicity to develop the disease probably due heritable factors. Diagnosis in people with Black ethnicity is more likely to be at a higher stage due in part to delayed diagnosis, limited access to treatment, systemic healthcare barriers, mistrust, and cultural factors. A family history of prostate cancer also significantly raises the risk.

Prostate cancer can be classified based on response to androgen deprivation therapy (ADT), which is described in the treatment pathway below. Prostate cancer can initially be responsive to hormone therapy and is referred to interchangeably as hormone-sensitive prostate cancer (HSPC) or castration-sensitive prostate cancer (CSPC). This project is in people with HSPC but it is useful to note that it may eventually become resistant to hormone therapy and is then referred to interchangeably as hormone-relapsed prostate cancer (HRPC) or castration-resistant prostate cancer (CRPC).

In some people, cancer cells break away from the prostate and travel through the bloodstream or lymphatic system to other areas like bones, lymph nodes, lungs, or liver. When the cancer has spread to other parts of the body, a person has metastatic disease, also known as stage 4 prostate cancer.

Assessing risk in metastatic prostate cancer involves evaluating the extent of cancer spread and its aggressiveness. This is typically done through imaging tests like bone scans, CT scans, and PSMA PET/CT scans, as well as assessing PSA levels and Gleason score. The information gathered helps determine the best treatment approach and prognosis. This was relevant for this appraisal because the marketing authorisation for abiraterone is for people with high-risk prostate cancer. As defined in LATITUDE, a pivotal abiraterone trial, a person is deemed to have high-risk prostate cancer if they have at least two of the three following factors:

1) Gleason score of 8 or higher;

2) the presence of three or more bone lesions;

3) measurable visceral metastasis.

The Gleason score is a system used to assess the aggressiveness of prostate cancer based on how abnormal the cancer cells appear under a microscope. The Gleason score ranges from 6 to 10, with higher scores indicating more aggressive cancer.

The presence of multiple bone lesions (three or more) signifies a significant burden of bone metastasis with increased risk of complications e.g. fractures and spinal cord compression. It also indicates more aggressive and widespread disease.

Measurable visceral metastasis in prostate cancer refers to the presence of measurable cancerous growths in internal organs (viscera), such as, the liver, lungs, or adrenal glands, detected during imaging scans. These metastases are typically found in advanced stages of prostate cancer and are associated with a poorer prognosis compared to bone-only metastases.

1.3. Current service provision

The first-line and second-line therapy options are detailed in the following sections. However, it is useful to note here that people are usually treated with ADT through all the lines of therapy.

1.4. First-line therapy

The EAG took advice from our clinical experts on the current treatment pathway for people with high-risk mHSPC. At the time of writing, the first-line treatments that can be offered in the NHS are described in Table 2.

Table 2: First line treatments currently offered on the NHS

Single therapy	Doublet therapies	Triplet therapy
ADT alone	docetaxel with ADT enzalutamide with ADT apalutamide with ADT abiraterone and prednisone* with ADT (via NHSE commissioning)	darolutamide with docetaxel and ADT

Abbreviations: ADT, Androgen Deprivation Therapy; NHSE, NHS England.

Note: *From this point forward in the report the EAG will refer to abiraterone and prednisone as abiraterone.

The initial decision is whether people should be offered ADT alone. There are two groups of people who could fall into this category. Firstly, there are the extremely frail who may not be offered intensified treatment. The average age of diagnosis is relatively old, but people in their 90s with performance status 3 or greater, might fall into this category. The other group are people with extremely indolent disease. Some people with metachronous disease, i.e.

metastatic disease diagnosed many years after primary treatment, with a very slow rising PSA and a very small burden of disease, may avoid treatment intensification if the risk of side effects and effects on quality of life are thought to outweigh benefits However, these two groups are a small proportion of people with mHSPC and people with extremely indolent disease are not categorised as high-risk.

In people who are able to have treatment intensification, a decision is taken whether to offer them triplet or doublet therapy. Triplet therapy is offered based on the burden of disease and ability to tolerate the therapy. Our clinical experts said that they would consider triplet therapy in people who have, for example, visceral metastatic disease such as liver metastasis or lung metastasis with nodes and bone metastasis. The ability to tolerate the therapy is primarily judged through age (ideally under 60 years old) and performance status (0 or 1). For example, people under the age of 60 with good performance status (0 or 1) would usually receive triplet therapy. The EAG's experts estimated that between 10-20% of people who receive treatment intensification for mHSPC would receive triplet therapy. The EAG received corroborating information from Peter Clark, the Cancer Drugs Fund Lead, that 18.6% of people who had treatment intensification for mHSPC received triplet therapy.

People for whom single agent therapy (ADT alone) or triplet therapy are not considered appropriate, receive doublet therapy. At the time of writing there were four doublet therapies available in the NHS: enzalutamide with ADT, apalutamide with ADT, abiraterone with ADT, and docetaxel (chemotherapy) with ADT. However, the EAG's experts explained that since the introduction of ARPIs into the treatment pathway, the use of docetaxel with ADT has been substantially reduced. Many people will choose not to have chemotherapy as it is recognised to have higher toxicity than ARPIs and has a big impact on quality of life. One expert explained that in their practice, it was very unlikely for people to be offered docetaxel with ADT without ARPI at first-line. There may a very small number who cannot have an ARPI who will be offered docetaxel with ADT at first line.

Therefore, the choice of doublet therapy first-line for people with mHSPC is between enzalutamide with ADT, apalutamide with ADT, and abiraterone with ADT. The NICE recommendation for apalutamide with ADT specifies people with mHSPC for whom docetaxel is not suitable. However, as noted above first-line usage of docetaxel with ADT has reduced since the introduction of ARPIs. Also, abiraterone's marketing authorisation is in people with high-risk mHSPC and therefore this appraisal concentrates on this as the relevant subgroup.

The EAG's experts explained that in people eligible for each of the three relevant doublet therapies, the decision of what to offer would be based on the side effects and co-morbidities of the person, as each ARPI has a different side-effects profile. Abiraterone can increase the risk of cardiac events, particularly in people with pre-existing cardiovascular disease, and as such, may be avoided in this population. A further concern with abiraterone is exposure of people to low dose, but long-term, steroids with prednisolone. The primary concerns specific to apalutamide and enzalutamide are in people who are prone to seizures as it crosses the blood-brain barrier and can reduce a person's seizure threshold. Also, both apalutamide and enzalutamide interact with medications, such as blood thinners and blood pressure medicines. If a person is on those medicines, it may be more appropriate to give a person abiraterone.

Peter Clark, the Cancer Drugs Fund Lead, disclosed the market share for people with mHSPC who had treatment intensification in the UK at the time of writing. In people who received doublet therapy (with ADT) 42.1% received enzalutamide, 43.9% received apalutamide, and 14.0% received abiraterone.

First-line therapy with ARPIs continues until there is evidence of progression. The EAG's experts noted that the definition of progression can vary between centres. Clinical progression is when people develop symptoms (including bone pain, urinary problems, fatigue, and weight loss), biochemical progression is when their Prostate-Specific Antigen (PSA) starts to rise, and radiological progression is when progression is visible on a scan. The experts estimated that on average first-line therapy continues for three to four years.

1.5. Second-line therapy

The second-line therapy a person can be offered is informed by the first-line therapy they received. NHSE Commissioning rules mean that people who received an ARPI at first-line cannot be re-challenged with an ARPI at second-line. People who received docetaxel chemotherapy first-line will not receive docetaxel chemotherapy at second-line, and will instead receive cabazitaxel chemotherapy if treatment with a taxane is considered the best option.

Based on these rules, the most common second-line option for people who had an ARPI with ADT at first line is docetaxel with ADT or ADT alone. People who received triplet therapy first-line are most likely to receive cabazitaxel chemotherapy with ADT or ADT alone at second-line. The EAG's experts noted that few people receive docetaxel with ADT first line, but for those

who did, second-line options would be an ARPI with ADT, cabazitaxel chemotherapy with ADT or ADT alone.

The EAG's experts also noted that, at the time of writing, there were further options for treating people if their disease has progressed to metastatic hormone-relapsed prostate cancer (mHRPC). In those cases, they would consider offering PARP inhibition with olaparib for people whose tumour has a BRCA mutation. Also, radium-223 can be used in the mHRPC population who have symptomatic bone metastases and no known visceral metastases and have already had docetaxel or docetaxel is contra-indicated or unsuitable.[8] Finally, enrolment in clinical trials may be considered.

2. DECISION PROBLEM

2.1. Background

The EAG have summarised the decision-problem detailed in the final scope as issued by NICE[9] and commented on where the methods in this analysis deviate from the scope. NICE instructed the EAG to undertake the project using a cost-comparison approach and the EAG's deviations from the final scope primarily relate to delivering a robust cost-comparison analysis.

2.2. Cost-comparisons

A cost comparison case can be made if a health technology is likely to provide similar or greater health benefits than technologies recommended in published NICE technology appraisal guidance for the same indication at a similar or lower cost.[10] NICE cost comparison appraisals use the assertion that if the treatment under investigation is found to be cost-effective versus the comparators, it is also cost-effective versus the comparators in the comparator's appraisals. This is relevant to this appraisal because other relevant treatments, such as ADT alone and docetaxel with ADT, have not been through the NICE technology appraisal process but were comparators in the appraisal of enzalutamide with ADT (TA712). Thus, if abiraterone with ADT is found to be cost effective versus enzalutamide with ADT, it is also cost effective versus ADT alone and docetaxel with ADT as the price and evidence base for these treatments has not had any major changes since TA712.

2.3. Decision problem

The EAG considered the population and interventions in the final scope to be appropriate. However, the EAG have deviated from the final scope in relation to the comparators. NICE listed all of the first-line treatments available in the NHS for first-line treatment of people with mHSPC. As noted in Section 2.2, the relevant comparators were treatments recommended in published NICE technology appraisal guidance for the same indication at a similar or lower cost. Three of the treatments detailed in the final scope had been recommended in published NICE technology appraisal guidance: enzalutamide with ADT; apalutamide with ADT; and darolutamide with docetaxel and ADT. However, as noted in Section 1.4, the decision of whether to offer triplet therapy (darolutamide with docetaxel and ADT) is taken before the decision of what doublet therapy to offer. Therefore, the decision of which doublet therapy to offer is between enzalutamide with ADT, apalutamide with ADT, and abiraterone with ADT, and

as such, enzalutamide with ADT and apalutamide with ADT were the relevant comparators for this appraisal.

The EAG's clinical experts agreed that the outcomes in the final scope were relevant to people with high-risk mHSPC. They noted that PFS is really important because it allows a person to avoid "the medicalisation" of their life. They can go on holiday with some tablets and have a hormone injection every three months. They do not have to see a doctor very often and are almost living a *normal* life. The EAG also included two outcomes relevant from an economic perspective in the protocol: time on treatment and time to discontinuation.

The EAG planned to conduct an economic analysis in-line with a cost comparison approach. However, as a pragmatic approach to explore the impact of assuming similar effectiveness, the EAG calculated the difference in effectiveness that would be needed to justify the difference in cost between abiraterone and the other treatments within scope and commented on the plausibility of this.

Table 3: Summary table of the decision problem

Item	Final protocol	EAG comments, including variation to the decision problem and rationale
Population	Adults with newly diagnosed high risk metastatic hormone-naive prostate cancer	Appropriate
Intervention	Abiraterone with prednisolone and ADT	Appropriate
Comparators	Traditional standard of care treatments: • ADT alone • Relugolix • docetaxel with ADT ARPIs: • enzalutamide with ADT • apalutamide with ADT • darolutamide with docetaxel and ADT • darolutamide with ADT (subject to NICE evaluation)	The two relevant comparators for the cost-comparison analysis have been bolded. These are the treatments that have been recommended in published NICE technology appraisal guidance and can be considered treatment options in people for whom triplet therapy (darolutamide with docetaxel and ADT) is not suitable. The EAG understood relugolix to be a treatment used as part of ADT and not as a relevant combination treatment in addition to ADT. ADT alone and docetaxel chemotherapy with ADT were not suitable comparators for the cost-comparison analysis. However, if abiraterone with ADT was

Item	Final protocol	EAG comments, including variation to the decision problem and rationale
		determined to have similar effectiveness, safety and similar or lower cost compared to enzalutamide with ADT, then given the prior decision by NICE, it would also be expected to be cost effective versus docetaxel chemotherapy with ADT and versus ADT alone.
Outcomes eligible for inclusion	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.	The EAG's clinical experts noted that OS and PFS are very important outcomes for people with mHSPC. PFS is really important because it allows a person to avoid "the medicalisation" of their life. The EAG also considered the following outcomes to be relevant for a cost comparison analysis: • time on treatment • time to discontinuation
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	NICE expected that a cost comparison was appropriate for this indication. The EAG checked these assumptions (particularly as the mechanism of action of abiraterone differs to the other ARPIs). As a pragmatic approach to test the impact of assuming similar effectiveness the EAG calculated the difference in effectiveness that would be needed to justify the difference in cost between abiraterone and the other treatments within scope and commented on the plausibility of this.

Item	Final protocol	EAG comments, including variation to the decision problem and rationale
	The availability and cost of biosimilar and generic products should be taken into account.	
Subgroups	No subgroups were detailed in the final scope	The EAG's experts did not note any subgroups relevant to this appraisal.
Special considerations including issues related to equity or equality	No special considerations detailed in the final scope	The EAG's experts did not note any special considerations including issues related to equity or equality relevant to this appraisal.

Abbreviations: ADT, androgen deprivation therapy; ARPIs, Androgen Receptor Pathway Inhibitors; EAG, external assessment group; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival.

3. TECHNOLOGIES

A brief overview of the technologies as described by the companies can be found in Table 4.

Please see the scope for further details.

Table 4: Description of technologies included in the assessment

Comparison	Apalutamide	Enzalutamide	Abiraterone and prednisolone
International non-proprietary name (Brand)	Erleada (apalutamide)	Xtandi (enzalutamide)	Zytiga (abiraterone) and Prednesol (prednisolone)
Principle pharmacological action and therapeutic class	*Apalutamide* is an androgen receptor (AR) inhibitor that works by directly binding to the ligand-binding domain of the AR. This binding prevents the AR from translocating to the cell nucleus, inhibits its ability to bind to DNA, and ultimately blocks AR-mediated gene transcription, thus hindering the growth and proliferation of prostate cancer cells.	*Enzalutamide* is an androgen receptor (AR) inhibitor that works by directly binding to the ligand-binding domain of the AR. This binding prevents the AR from translocating to the cell nucleus, inhibits its ability to bind to DNA, and ultimately blocks AR-mediated gene transcription, thus hindering the growth and proliferation of prostate cancer cells.	*Abiraterone* is an ARPI which inhibits CYP17 enzymes to block androgen biosynthesis in the testes, adrenals, and tumour tissue, thereby reducing testosterone to undetectable levels. *Prednisolone* is a synthetic glucocorticoid
Course of treatment	Recommended dose: 240 mg as an oral single daily dose. If a ≥ Grade 3 toxicity or an intolerable adverse reaction is experienced by the person, dosing should be held rather than permanently discontinuing treatment until symptoms improve to ≤ Grade 1 or original grade, then should be resumed at the same dose or a reduced dose (180 mg or 120 mg), if warranted. No dosing adjustment for elderly, renal impairment, or hepatic impairment.	Recommended dose: 160 mg/day. Dose can be reduced (120 mg or 80 mg) due to toxicity.	Recommended dose: 1,000 mg (four 250 mg tablets) as a single daily dose that must not be taken with food. It is used with 10 mg prednisone or prednisolone daily. Abiraterone can be reduced to 500 mg due to hepatotoxicity.
Proposed/approved indications	Apalutamide is indicated for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT).	Enzalutamide is indicated for the treatment of adults with mHSPC in combination with androgen deprivation therapy.	Abiraterone acetate is indicated with prednisone or prednisolone for the treatment of newly diagnosed High-risk mHSPC in adults in combination with ADT.
Toxicities (or other characteristics) that may	The most common adverse reactions are fatigue (26%), skin rash (26% of	The most common adverse reactions are asthenia/fatigue, hot flush,	*Abiraterone*: adverse reactions: peripheral oedema, hypokalaemia,

Comparison	Apalutamide	Enzalutamide	Abiraterone and prednisolone
result in differences in use	any grade and 6% Grade 3 or 4), hypertension (22%), hot flush (18%), arthralgia (17%), diarrhoea (16%), fall (13%), and weight decreased (13%). Other important adverse reactions include fractures (11%), decreased appetite (11%) and hypothyroidism (8%).	hypertension, fractures, and fall. Other important adverse reactions include ischemic heart disease and seizure.	hypertension, urinary tract infection, and ALT increased. Other important adverse reactions include, cardiac disorders, hepatotoxicity, fractures, and allergic alveolitis. *Prednisolone:* examples include Kaposi's sarcoma, schizophrenia and epilepsy.
Interaction with other medicinal products and other forms of interaction	CYP2C8/ CYP3A4 play a role in the elimination of apalutamide and in the formation of its active metabolite. A reduction of the apalutamide dose based on tolerability should be considered Apalutamide is a potent enzyme inducer and increases the synthesis of many enzymes and transporters; therefore, interaction with many common medicinal products that are substrates of enzymes or transporters is expected. The reduction in plasma concentrations can be substantial, and lead to lost or reduced clinical effect.	CYP2C8 plays an important role in the elimination of enzalutamide and in the formation of its active metabolite. If people must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily. Enzalutamide is a potent enzyme inducer and increases the synthesis of many enzymes and transporters; therefore, interaction with many common medicinal products that are substrates of enzymes or transporters is expected.	Caution is advised when administering with medicinal products activated by or metabolised by CYP2D6, particularly with medicinal products that have a narrow therapeutic index. Dose reduction of medicinal products with a narrow therapeutic index that are metabolised by CYP2D6 should be considered. In a CYP2C8 drug drug interaction trial in healthy subjects, the AUC of pioglitazone was increased by 46% and the AUCs for M III and M IV, the active metabolites of pioglitazone, each decreased by 10% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate. Patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly.
Any differences that may result in different populations using the medicine	This therapy does not require concomitant steroid treatment.	This therapy does not require concomitant steroid treatment.	People unable to take steroids cannot use this therapy.

Abbreviations: ADT, androgen deprivation therapy; ALT, Alanine Aminotransferase; AR, androgen receptor; ARPIs, Androgen Receptor Pathway Inhibitors; DHT, dihydrotestosterone; HR, high risk; LHRH, Luteinizing Hormone-Releasing Hormone; mHSPC, metastatic hormone sensitive prostate cancer.

4. CLINICAL AND TECHNOLOGICAL EVIDENCE SELECTION

4.1. Approach

As previously stated, a cost comparison case can be made if a health technology is likely to provide similar or greater health benefits than technologies recommended in published NICE technology appraisal guidance for the same indication at a similar or lower cost. The EAG conducted a clinical effectiveness and safety systematic literature review (SLR) and network meta-analysis (NMA), including relevant comparators, to support an assessment of whether combination therapy with abiraterone with ADT offers a similar benefit to doublet therapy with enzalutamide with ADT and apalutamide with ADT. The SLR followed the general principles published by the Centre for Reviews and Dissemination (CRD) at the University of York.[11]

4.2. Inclusion criteria

The inclusion and exclusion criteria for the clinical effectiveness and safety SLR are shown in Table 5. These criteria were informed by the final scope issued by NICE and discussion between the EAG and the NICE team. The criteria have also been informed by the need to capture the key evidence for the purposes of the assessment objectives. The inclusion criteria are consistent with the decision problem for this assessment (Section 2.3).

Table 5: Inclusion and exclusion criteria, clinical effectiveness

	Inclusion criteria	Exclusion criteria
Population	Adults with newly diagnosed high-risk metastatic hormone-sensitive prostate cancer. Where high-risk populations were not available, data in adults with metastatic hormone-sensitive prostate cancer were used.	Adults with metastatic hormone-resistant prostate cancer.
Intervention	Oral abiraterone 1,000 mg as a single daily dose used with 5 mg of prednisone or prednisolone daily.	
Comparators	• ADT alone • enzalutamide with ADT • apalutamide with ADT	
Outcomes	• overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life • time on treatment • time to discontinuation	
Study design	Stage 1 • Systematic reviews and network meta-analyses Stage 2 • RCTs	• Observational studies • Case control studies • Cross-sectional studies • Conference abstracts without the accompanying poster or slide presentation, or without a sister, full-text publication from the same study.
Language	English	Studies not reported in English

Abbreviations: ADT, androgen deprivation therapy; mg, milligram; RCT, randomised controlled trial.

4.3. Evidence search strategies and study selection

The clinical evidence searches sought to identify reports of the effectiveness and safety of the intervention and comparators, with a view to the implementation of an NMA. Database searches were performed in Medline, Embase, Cochrane CENTRAL, Cochrane Database of Systematic Reviews, and INAHTA. Trial protocols were identified from searches in ClinicalTrials.gov, the International Clinical Trials Registry Platform (ICTRP), Embase, and Cochrane Protocols. We took a pragmatic approach to the acquisition of evidence, with the idea of building on, rather than repeating, previous systematic reviews. With this in mind, we first searched for pre-existing SLRs and NMAs. After having identified the most recent NMA, we then performed an RCT search for trials published after the date of the NMA search.

This search approach, and its rationale, is fully described in the published protocol. No amendments to the planned search process were made. Details of the search approach, including lists of databases, search strategies and outcomes can be found in Appendix A. Screening took place in Rayyan[12] and was performed using the inclusion and exclusion criteria described in the published protocol. A PRISMA diagram of the search and screen process for SLRs and NMAs is provided in Appendix B.

The SLR/MA clinical search retrieved 530 articles. Of these, 69 were selected for full text screening. Of these, one full text was unavailable and 52 were excluded, leaving 17 includes. Reasons for exclusion can be seen in Appendix C.

The most recent NMA was Wang et al. (2024),[13] whose search identified studies up to 14 June 2024. We therefore performed the RCT update search from 1 January 2024 to the present day (27 June 2025). The RCT search approach (dates) retrieved 870 articles (including 50 registry records of ongoing studies, from Embase, ClinicalTrials.gov and the ICTRP). 858 were excluded at TIAB, leaving 12 for full text appraisal. All 12 were excluded at full text. A PRISMA diagram of the RCT search and screen process can be found in Appendix B. Reasons for exclusion can be seen in Appendix C.

4.4. Included and excluded studies

The four RCTs included in the analysis are detailed below in Table 6.

Table 6: Key studies with clinical and technological evidence

Study name, design and location	Interventions and comparator	Participants and setting length of follow-up	Relevant outcomes and key results	EAG comments
ARCHES[14,15] NCT02677896 Double-blind, phase III, RCT 283 centres in North and Latin America, Europe, and Asia Armstrong 2019 Armstrong 2022 (OLE)	Enzalutamide with ADT (n=574) versus placebo with ADT (n=576)	N=1150. Adults with mHSPC ECOG status score of 0 or 1 Up to six cycles of prior docetaxel chemotherapy were permitted. Median FU: 14.4 months until treatment unblinded. OLE FU (treatment changing permitted): 44.6 months	At 14.4 months: • OS • rPFS (HR subgroup) • Time to deterioration of QoL • Grade ≥3 AEs • Hypertension (Grade ≥3) • Fatigue (all grades) At 44.6 months (OLE): • OS (Gleeson score >7) • rPFS • Grade ≥3 AEs • Hypertension (Grade ≥3) • Fatigue (all grades)	The population recruited to the trial did not all have high-risk prostate cancer. Relevant subgroup analysis was used when available. After unblinding, 180 (31.3%) people randomised to placebo with ADT crossed over to enzalutamide with ADT.
LATITUDE[16,17] NCT01715285 Double-blind, phase III, RCT 235 centres in 34 countries across Europe, the Asia–Pacific region, Latin America, and Canada Fizazi 2017 Fizazi 2019 (OLE)	Abiraterone acetate and prednisone with ADT (n=597) versus placebo with ADT (n=602)	N=1199 Adults with High-risk mHSPC ECOG status score of 0–2 No prior treatment with docetaxel chemotherapy was permitted. Median FU: 30.4 months until treatment unblinded. OLE FU (treatment changing permitted): 51.8 months	At 30.4 months: • OS • rPFS • Time to deterioration of QoL • Grade ≥3 adverse events • Hypertension (Grade ≥3) • Fatigue (all grades) At 51.8 months (OLE): • OS • Grade ≥3 adverse events • Hypertension (Grade ≥3) • Fatigue (all grades)	The population recruited had high-risk mHSPC with no previous docetaxel treatment. At the time of final analysis, 72 (12.0%) people randomised to placebo with ADT crossed over to abiraterone with ADT.

Study name, design and location	Interventions and comparator	Participants and setting length of follow-up	Relevant outcomes and key results	EAG comments
STAMPEDE[18-20] NCT00268476 Open-label, phase III, RCT 120 centres in UK and Switzerland James 2017 (HSPC) Hoyle 2019 (high-risk mHSPC subgroup) Attard 2023 (mHSPC subgroup)	Abiraterone acetate and prednisone with ADT (n=960) versus ADT alone (n=957)	N=1917 Adults with HSPC WHO status score of 0-2 No prior treatment with docetaxel chemotherapy was permitted. Median FU 40 months at the first analysis and at 96 months in the final analysis.	At 40 months: • OS (metastatic HR) • PFS (metastatic HR) • Grade ≥3 adverse events • Hypertension (Grade ≥3) • Fatigue (all grades) At 96 months: • Grade ≥3 adverse events • Hypertension (Grade ≥3) • Fatigue (all grades)	The trial recruited a wider population (HSPC). Subgroup analysis in people with high-risk mHSPC has been used where available. The trial reported PFS rather than rPFS This trial did not have an OLE and no crossing over from comparator to intervention reported.
TITAN[21,22] NCT02489318 Double-blind, phase III, RCT 229 centres in North and Latin America, Europe, Asia, and Australia. Chi 2019 Chi 2021 (OLE)	Apalutamide with ADT (n=525) versus Placebo with ADT (n=527)	N=1052 Adults with mHSPC ECOG status score 0-1 Prior docetaxel chemotherapy was permitted. Median FU: 22.7 months until treatment unblinded. OLE FU (treatment changing permitted): 44.0 months	At 22.7 months: • OS (Gleason score ≥8) • rPFS (Gleason score ≥8) • Grade ≥3 adverse events • Hypertension (Grade ≥3) • Fatigue (all grades) At 44.0 months: • OS (HR) • Grade ≥3 adverse events • Fatigue (all grades)	The population recruited to the trial did not all have high risk prostate cancer. Relevant subgroup analysis was used where available. After unblinding, 208 (39.5%) people randomised to placebo with ADT crossed over to apalutamide with ADT.

Abbreviations: ADT, androgen deprivation therapy; AEs, adverse events; ECOG, Eastern Cooperative Oncology Group; FU, follow-up; HR, high-risk; mHSPC, metastatic hormone-sensitive prostate cancer; OLE, open-label extension; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RCT, randomised controlled trial; rPFS, radiographic progression-free survival.

5. CLINICAL AND TECHNOLOGICAL EVIDENCE REVIEW

5.1. Quality appraisal of studies

Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2)[23] was used to assess the risk of bias in in the trials included in the NMAs. Risk of bias was evaluated for each specific result reported in a RCT, rather than assessing the entire trial at once. A summary of the judgments as they pertained to specific trials results is presented in the following sections.

5.1.1. Randomisation process

All outcomes for all four of the trials were judged to be at low risk of bias for randomisation process. They each presented valid methods of randomisation and valid methods of concealment of treatment allocation from those enrolling participants and assigning treatments. Within each trial there were no differences between treatment arms in baseline characteristics to suggest random allocation was not achieved.

However, the population of interest for this appraisal were people with high-risk mHSPC and LATITUDE was the only trial where only people with high-risk cancer were included. Therefore, the NMAs often used subgroup analysis from the trials where appropriate to better match the high-risk mHSPC population.

A number of the NMAs used subgroup analysis from the ARCHES trial. This was either the high-risk mHSPC subgroup or the subgroup of people with mHSPC who had a Gleason score ≥8 (a criteria for high-risk tumours) where data specifically in the high-risk subgroup were not available. The EAG's experts agreed that Gleason score of 8 or higher is an indicator of high-risk cancer but mentioned that it was only one of three criteria. The trial was not stratified by either of these subgroups and, as such, randomisation was broken by these analyses. Similarly, the high-risk mHSPC subgroup was reported for the STAMPEDE trial but the trial was not stratified by the high-risk mHSPC subgroup and randomisation was broken by these analyses. STAMPEDE presented baseline characteristics of the two arms in the high-risk mHSPC subgroup and this has been reproduced in Table 56 in Appendix D. The intervention and comparator arms were similar for most baseline characteristics presented with minor differences for PSA level and T stage. However, despite the apparent similarity of measured baseline characteristics in STAMPEDE, the EAG had some concerns over the risk of bias related to the breaking of randomization in the subgroup analysis in both trials.

TITAN presented subgroup analysis (Gleason score ≥8) but the trial was stratified by Gleason score ≥8 and, as such, did not break randomisation.

5.1.2. Deviations from the intended interventions

ARCHES, LATITUDE, and TITAN were double-blind trials and there was no indication of notable deviations from the intended interventions within the randomised period of each trial. Therefore, outcomes measured in that period were judged to be at a low risk of bias for this domain. STAMPEDE was an open-label trial and the EAG had some concerns that this could have led to deviations from the intended treatment.

ARCHES, LATITUDE, and TITAN also had open-label extensions (OLEs) after the randomised period of the trial was completed. When the OLE period began people in the comparator arm who were alive and had not progressed were eligible to cross over to the intervention treatment. Therefore, there was a substantial deviation from the randomised interventions for outcomes measured in the OLE periods of ARCHES, LATITUDE, and TITAN. These outcomes were at high risk of bias for this domain.

5.1.3. Missing outcome data

All of the four trials reported less than 10% missing data for all outcomes in both the randomised period, and where applicable, the OLE periods. The EAG judged all outcomes to be at low risk of bias for this domain.

5.1.4. Measurement of the outcome

The definitions of OS were standard across all trials included in the NMAs.

The definitions of rPFS were similar across ARCHES, LATITUDE, and TITAN and each included regular radiographic assessment of progression in participants. LATITUDE defined rPFS as radiographic progression of soft-tissue lesions was evaluated by either CT or MRI on the basis of RECIST, version 1.1. Progression on bone scanning was assessed by adaptation of Prostate Cancer Working Group 2 criteria.[24] People were given a CT or MRI every 2 months. STAMPEDE reported PFS, rather than rPFS, and the EAG included the trial in the rPFS NMA based on use of the trial in previous appraisal analysis (TA721). PFS in STAMPEDE was defined as time from randomisation to the first of: new disease or progression of: distant metastases, lymph nodes or local disease; or death from prostate cancer. People had scans or X-rays repeated at 24 weeks if they were abnormal at baseline, or when clinically appropriate.

The EAG considered STAMPEDE data to be at high risk of bias in the rPFS NMA due to the measurement of the outcome.

The EAG also noted that the number of people reporting fatigue (all grades) was notably higher in both treatment arms in STAMPEDE than the other trials, including LATITUDE, the other abiraterone trial. All four trials graded and summarised adverse events using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)[25] and it was unclear to the EAG why higher proportions of people in STAMPEDE were found to have experienced fatigue. Given the unaccounted-for difference, even between the number of people with fatigue (all grades) in the comparator arm in STAMPEDE and the comparator arms in the other trials, the EAG had some concerns over the fatigue results of STAMPEDE.

Nothing in the trial reports suggested measurement of ascertainment of the outcome differed between treatment arms.

5.1.5. Selection of the reported result

Each of the trials reported OS and rPFS/PFS as detailed in the trial protocols in the full trial populations. However, the population of interest for this appraisal were people with high-risk mHSPC, and LATITUDE was the only trial where only the relevant population were recruited.

The three other trials recruited a broader population and subgroup analysis was used in the NMA to better match the relevant high-risk mHSPC population. When trials prespecified subgroup analyses they plan to report it is normally not judged to be a risk of bias. When trials report subgroup analyses that were not pre-specified it can be a risk of bias because they are searching for a positive effect. The more subgroups analysed, the higher the chance of encountering a statistically significant effect due to random variation rather than a true effect.

Subgroup analysis was presented in ARCHES and TITAN and these subgroup analyses were pre-specified and, as such, were not at a risk of bias. STAMPEDE did not prespecify high-risk mHSPC and, as such, may be at a risk of bias. However, the EAG considered it quite reasonable that, given the marketing authorisation for abiraterone, trials of abiraterone would report the efficacy of treatment in the relevant (high-risk mHSPC) population post hoc.

5.2. Indirect comparison methods

The methods and trials used in the indirect comparison are reported in this section.

5.2.1. Characteristics and appraisal of trials identified and included in the indirect comparisons

5.2.1.1. Treatments received during the trials and subsequent to the trials

As detailed in Table 5 in Section 4.4, three (ARCHES, LATITUDE, and TITAN) of the four trials included in the NMA reported outcomes after an initial randomised phase and then became open label extensions (OLE) where people in the placebo arm who survived, and whose cancer had not progressed, were permitted to have the trial intervention until the trial ended. The fourth trial in the NMA was STAMPEDE where people in the placebo arm did not cross over to the trial intervention after an initial analysis. The time until crossover and the number of people who crossed over is detailed below in Table 7.

In light of the varying follow-up and the permitted crossover of treatment from the placebo arm to the intervention arm, the EAG have undertaken NMAs at two different timepoints for each outcome. The first round of NMAs used datacuts reported up to a median follow-up of 40 months. These datacuts were prior to the OLEs in ARCHES, LATITUDE, and TITAN beginning and before any treatment crossover was formally permitted.

A second round of NMAs was run using the latest datacut reported for each of the trials where in the OLEs people were permitted to crossover from placebo to the intervention. For all NMAs we used intention-to-treat (ITT) data where people were analysed in the initial treatment group to which they were randomised. However, the EAG caution that the time until crossover, when crossover was permitted, varied widely across the trials. The comparator arm in ARCHES received placebo and ADT for a median 14.4 months before cross-over was permitted which led to 31.3% of participants receiving open-label treatment with enzalutamide with ADT (median time until cross-over = 21.5 months). A larger proportion of participants in TITAN crossed over to apalutamide with ADT (39.5%) compared to ARCHES although the median time until cross-over was not reported. Given the variation between the trials in terms of the time until crossover was permitted and the number crossing over to the intervention treatment, along with uncertainty related to the period participants received the comparator treatment, the EAG cautioned that the treatment crossover influenced all of the outcomes presented in the analysis of latest trial data after unblinding. A higher proportion of participants in ARCHES (enzalutamide) and TITAN (apalutamide) crossed over than did in LATITUDE (abiraterone) to the intervention and therefore they were most at risk of underestimating the effectiveness of the intervention.

Table 7: Crossover from placebo to intervention

Trial	Intervention	Time until crossover was permitted	No (%) of people in the comparator arm who crossed over prior to disease progression
ARCHES	Enzalutamide	14.4 months	180 (31.3%)
LATITUDE	Abiraterone	30.4 months	72 (12.0%)
STAMPEDE	Abiraterone	Not permitted	0
TITAN	Apalutamide	22.7 Months	208 (39.5%)

In addition to the treatment crossover permitted in the OLEs, each of the four trials varied in terms of the first subsequent prostate cancer treatments trial participants received after disease progression (Table 8).

A higher proportion of people in the intervention (abiraterone) arms of LATITUDE and STAMPEDE received docetaxel chemotherapy than the intervention arms in ARCHES or TITAN. This may have been due to ARCHES and TITAN including a proportion of participants who had previously been given docetaxel chemotherapy for prostate cancer. In the comparator arms (placebo with ADT / ADT alone) 65.0% of participants in TITAN received docetaxel chemotherapy, followed by 50.1% in LATITUDE, and fewer in STAMPEDE and ARCHES. It was unclear to the EAG why so many more participants in TITAN were treated with docetaxel chemotherapy second-line.

The proportion of people receiving cabazitaxel was low across all arms in all four trials. It was similar (6% to 9% of those who received subsequent therapy) in LATITUDE, STAMPEDE, and ARCHES. Only 2 (1.7%) people in the apalutamide arm in TITAN. The use of cabazitaxel in the comparator arms ranged from 30 (8.0%) participants in LATITUDE down to 6 (2.7%) in ARCHES.

A slightly higher proportion of people who received subsequent therapy in the intervention arms of TITAN (30%) and ARCHES (25.2%) received ARPI therapy (abiraterone or enzalutamide) compared to LATITUDE (23.8%) and STAMPEDE (16.8%). STAMPEDE was notably lower but this may be due to the trial primarily occurring in the UK where re-treatment with ARPIs was not common practice. The EAG noted that there is evidence that people can gain resistance to these treatments[26] and, given the similarity in the mechanism of action of ARPIs, if a person's

cancer stops responding to one, it probably won't respond to another.[27] Therefore, these differences in later ARPI therapy would be unlikely to bias the results.

In sum, the EAG cannot draw any firm conclusions from these differences in subsequent treatments but understand that it added a layer of uncertainty to the estimate of effect for OS especially at the later timepoints.

Table 8: First subsequent antineoplastic therapy for prostate cancer (not including OLE crossovers)

	LATITUDE (30.4 months)		**STAMPEDE** (40.0 months)		**ARCHES** (44.6 months)		**TITAN** (44.0 months)	
	Abi+ADT (n=597)	PBO+ADT (n=602)	Abi+ADT (n=960)	ADT (n=957)	Enza+ADT (n=574)	PBO+ADT (n=576)	Apa+ADT (n=525)	PBO+ADT (n=527)
Received further antineoplastic therapy	168 (28.1%)	373 (62.0%)	196 (20.4%)[1]	477 (49.8%)[1]	131 (22.8%)[2]	221 (38.4%)[2]	120 (48.6%)[1]	221 (64.1%)[1]
Number who subsequently received specified antineoplastic therapies of interest (%)								
Docetaxel	106 (17.8%)	187 (31.0%)	115 (12.0%)	200 (20.9%)	48 (8.4%)	71 (12.3%)	42 (8.0%)	78 (1.5%)
Enzalutamide	30 (5.0%)	76 (12.6%)	25 (2.6%)	138 (23.1%)	7 (1.2%)	61 (10.6%)	9 (1.7%)	24 (4.6%)
Apalutamide	0	0	0	0	0	0	0	0
Abiraterone	10 (1.7%)	53 (8.8%)	8 (0.8%)	120 (12.5%)	26 (4.5%)	42 (7.3%)	27 (5.1%)	65 (12.3%)
Cabazitaxel	11 (1.8%)	30 (5.0%)	15 (1.6%)	28 (4.7%)	11 (1.9%)	6 (1.0%)	2 (0.4%)	5 (0.9%)
Radium-223	11 (1.8%)	27 (4.5%)	19 (2.0%)	24 (4.0%)	6 (1.0%)	4 (0.7%)	5 (1.0%)	5 (0.9%)

Abbreviations: ADT, androgen deprivation therapy; OLE, open-label extension; PBO, placebo; NE, not estimable; NR, not reported.

[1] The trial specified the number of people who reported a new treatment. This was not limited to antineoplastic therapy.

[2] The subsequent antineoplastic therapies received were not limited to the therapies specified in this table

5.2.2. Populations recruited to the trials

The relevant population for this trial were people with high-risk mHSPC. This is because the marketing authorisation for abiraterone was limited to a high-risk population, as defined in LATITUDE (1.2.2). The EAG have made it clear in the results where subgroup analysis from the other trials were used in the NMAs.

5.2.3. Network meta-analyses (NMAs) of main outcomes

NMAs were undertaken where possible given the outcome data presented for the four trials in the network. There were sufficient data to conduct NMAs for OS, rPFS, HRQoL, and adverse events. On the advice of our clinical experts we completed NMAs for adverse events Grade 3-5, fatigue (all grades), and hypertension (Grade 3-5). They reasoned that all fatigue can impact on quality of life. It was not possible to extract sufficient data from the trials to conduct NMAs for response rate, time on treatment, or time to discontinuation. The input data used in the NMA and baseline characteristics of participants in the trials are detailed in Appendix D.

NMA models were fitted to trial-level reported data for the outcomes of main interest listed in Table 4 using the Bayesian approach to inference. For time-to-event data such as OS and rPFS, this was done under the assumption of proportional hazard functions for different treatment arms (Section 5.2.4) and the NMA models were fitted to the logarithms of the hazard ratios using the inverse-variance method. For binary outcomes, such as the occurrence of at least one specific adverse event in a given time period, the NMA models were fitted to the logarithms of the odds ratios using the inverse-variance method. Two models were fitted for each outcome based on the data cuts from the trials. Analysis of latest trial data up to a 40-month follow-up used the trial data at the latest data cuts of ARCHES, LATITUDE, and TITAN prior to the OLEs beginning and the STAMPEDE 40-month median follow-up. Analysis of latest trial data after unblinding used the final data cuts from each of the trials including the OLEs in ARCHES, LATITUDE, and TITAN.

Apart from the analyses just discussed, a sensitivity analysis of each NMA of main interest was performed, where possible, with data for high risk mHSPC patients replaced by data for all mHSPC patients. These latter analyses were conducted to check whether the use of data for all mHSPC patients was acceptable as a surrogate for high risk mHSPC patient data in the main analyses and also to gauge the general sensitivity of results to cancer risk classification. This was necessary because for some trials no data were presented in people with high-risk mHSPC

and either the full trial data or approximate subgroup data (Gleason score ≥8) were used in the analyses.

For all analyses, the NMAs models were fitted separately under the assumptions of fixed and random treatment effects, where possible, otherwise only fixed effects NMA was performed.[28] Non-informative prior distributions were used for the main treatment effects and reasonable approximations to non-informative prior distributions were used for the variance of the random treatment effect where applicable. Model fit and algorithm convergence were checked using standard methods. Cochran's Q tests for heterogeneity were conducted on trial results for individual treatment comparisons where appropriate. As none of the analyses were performed on the basis of an NMA graph that contained closed loops, standard NMA consistency checks were not applicable.

5.2.4. Investigation of the proportional hazards assumption

The proportionality of hazard functions for the different arms of each trial included in the NMA were investigated in the standard way by using plots of non-parametric estimates and 95% confidence bands of the logarithm of the hazard ratio between treatment arms over time. These plots were supplemented by chi-squared tests of the correlation of the Schoenfeld residuals over time and log cumulative hazard plots (also known as log minus log survival plots) of each treatment. The individual patient survival data that was required for these analyses was obtained by digitising Kaplan-Meier curves for the relevant outcome that appeared with the published trial results using the R package IPDfromKM (https://CRAN.R-project.org/package=IPDfromKM). The data used was the latest data cut in each of the trials prior to any subsequent removal of blinding.

The results of this analysis showed that the plots of the estimated logarithm of the hazard ratio over time were consistent with the hazard ratio being a constant, since this hypothesis lay within the 95% confidence bands of the estimated log hazard ratio function for all trials and for both of the outcomes of progression-free survival and overall survival (see the corresponding figures in Appendix E). For all trials and for both of these outcomes, the plots of the log cumulative hazard functions were parallel enough between treatment groups over periods of time with the highest frequency of events to conclude that the assumption of proportional hazard functions holds (see the corresponding figures in Appendix E). Taken as a collection of significance tests, there was not a strong indication from the results of the chi-squared tests of the correlation of the

Schoenfeld residuals over time for each of the analyses concerned to conclude that the proportional hazards assumption fails (see the corresponding test results in Appendix E).

In summary, the results of an investigation of the assumption of proportional hazard functions between trial arms gave no evidence beyond usual sampling variability of a failure of this assumption with regard to overall survival or progression-free survival for any of the four included trials. Therefore, this justifies analysing the time-to-event data concerned using a proportional hazards survival model.

5.2.5. Effect modifiers across the network

The EAG noted that across the relevant previous appraisals (TA712, TA721, TA741) the baseline characteristics focussed on were: Gleason score, ≥3 bone metastases at screening, distant metastasis at initial diagnosis, time since diagnosis with mHSPC, and ECOG/WHO Performance status. The EAG's clinical experts considered these to be prognostic factors rather than effect modifiers. They understood the only known effect modifier to be age (people >75 years old benefit less) as suggested by the STOPCAP analysis.[29] STOPCAP used individual participant data for completed trials, including among others LATITUDE, STAMPEDE, and TITAN, examining effects of androgen receptor pathway inhibitors for mHSPC.

The effect modifiers and prognostic factors of the participants in each trial are presented in Table 9. Each of the trials reported median age at randomisation. The median ages of the participants in the trials was as high as 70 in ARCHES with slightly lower, either 67 or 68, in the other trials. While the difference in median age was small it resulted in 29.5% of participants in ARCHES being at least 75 years old compared to 23.4% in TITAN and 20.3% in LATITUDE. The EAG understood this small difference in median age may have led to enzalutamide having a reduced apparent effectiveness in the NMA. However, it unclear to the EAG what the magnitude of the effect of having between 7% and 10% more 75 year olds would be.

Outside of age, the reporting of these factors was inconsistent and in most cases the participants in the subgroup of interest (high-risk mHSPC) were not presented. In the instance where this was presented, i.e. the LATUITUDE participants and the relevant STAMPEDE subgroup, the LATITUDE trial had a higher proportion of people with and ECOG/WHO performance status score of one or more. This indicated participants in LATITUDE had a greater degree of functional impairment and dependence at the start of the trial. However, the EAG noted that this did not have a large effect as the efficacy results of the trials were similar.

Overall, the EAG was largely unable to find and compare the effect modifiers and prognostic factors across the relevant participants (high-risk mHSPC) in each trial and, as such, there was uncertainty as to whether the trials were well balanced for these factors. As previously stated, the EAG's experts considered only age to be a treatment effect modifier and that potentially led to an underestimation of the enzalutamide treatment efficacy. However, the difference between the trials was small and the EAG did not consider this was likely to have had a large effect on the results of the NMA. There were differences in prognostic factors between the trials but these were not found to be treatment effect modifiers in the STOPCAP analysis[29] and, as such, would not be expected to lead to confounding of the indirect estimates.

Table 9: Summary information for select effect modifiers and prognostic factors

Trial name	Age (median)	High-risk factors[a], n (%)			Days since diagnosis with mHSPC, median (IQR)	Distant metastasis at initial diagnosis, n (%)	ECOG performance status score: 1+, n (%)
		Gleason score ≥8	3+ bone lesions	Visceral disease			
ARCHES mHSPC (Enzalutamide)[15]	70 | 70 (29.5% ≥75)	386 (67.2)	NR	64 (11.1) | 64 (11.1)	NR	402 (70.0) | 365 (63.4)	125 (21.8) | 133 (23.1)
ARCHES high-risk mHSPC (Enzalutamide)[15]	NR	NR	NR	NR	NR	NR	NR
LATITUDE High-risk mHSPC (abiraterone)[17]	68 | 67 (20.3% ≥75)	584 (98) | 586 (97)	586 (98.2) | 585 (97.2)	NR	1.08 | 1.08 months[b]	NR	271 (45.4) | 271 (45.0)
STAMPEDE HSPC (abiraterone)[30]	67 | 67 (≥75 NR)	715 (74) | 721 (75)	NR	NR	77 (57-101) | 79 (57-100)[d]	465 (48) | 476 (50)	213 (22) | 215 (22)[c]
STAMPEDE mHSPC (abiraterone)[20]	67 | 67 (≥75 NR)	366 (76.1) | 374 (74.5)	NR	NR	77 (54–97) | 71 (51–95)[d]	NR	125 (25.0) | 132 (26.3)[c]
STAMPEDE high-risk mHSPC (abiraterone)[19]	67 | 67 (≥75 NR)	239 (99.2) | 229 (98.7)	NR	20 (8.3) | 25 (19.8)	NR	NR	64 (26.6) | 69 (29.7)[c]
TITAN mHSPC (apalutamide)	69 | 68 (23.4% ≥75)	351 (66.9) | 358 (67.9)	NR	56 (10.7) | 72 (13.7)	3.5 | 3.41 months[d]	411 (78.3) | 441 (83.7)	197 (37.5) | 178 (33.8)
TITAN high-risk mHSPC (apalutamide)	NR	NR	NR	NR	NR	NR	NR

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HSPC, hormone-sensitive prostate cancer; IQR, interquartile Range; mHSPC, metastatic hormone-sensitive prostate cancer; NR, not reported; PSA, Prostate-Specific Antigen
where results were available by arm the figures are shown separated by a bar (|).
[a] People with at least two of these factors have high-risk cancer
[b] Time from GnRH agonist/antagonist to first dose, (months)
[c] WHO performance status, 0 or 1
[d] Median time from initial diagnosis to randomization

5.2.6. Time on treatment in the trials

It was not possible to run an NMA using the time-on-treatment reported in the trials but the results of what the EAG could find are reported in Table 10 as they are used in the economic analysis. Prior to OLEs time on treatment was substantially lower in the ARCHES trial (12.8 months) than the other trials. When taking into account the OLEs, time on treatment was shorter in the trials of abiraterone (25.8 months and 33.2 months) as compared to enzalutamide (40.2 months) and apalutamide (39.3 months). However, these data are not directly comparable as the data from LATITUDE (25.8 months) was taken from a high-risk mHSPC population whereas the other trial estimates were in people with (high-risk and not high-risk) mHSPC.

The EAG noted that the NMA found people on abiraterone were more likely to have Grade 3+ adverse events (AEs) than people on enzalutamide or apalutamide and posited to the clinical experts that higher serious AEs may have led to shorter time on treatment. However, the EAG's clinical experts considered that in their practices abiraterone had similar tolerability to enzalutamide and apalutamide. In sum, the EAG understood the shorter time on treatment to have occurred in LATITUDE because it was a high-risk population but it was unclear why the mHSPC subgroup in STAMPEDE had shorter time-on-treatment than the ARCHES (enzalutamide) or TITAN (apalutamide) OLEs.

Table 10: Time on treatment

Trial name	Intervention given with ADT	Median follow-up period	Median time on treatment
ARCHES	Enzalutamide	14.4 months	12.8 months
ARCHES OLE	Enzalutamide	44.6 months	40.2 months
LATITUDE	Abiraterone	30.4 months	24 months
LATITUDE OLE	Abiraterone	51.8 months	25.8 months
STAMPEDE: HSPC	Abiraterone	40 months	23.7 months
STAMPEDE: mHSPC	Abiraterone	40 months	33.2 months
TITAN	Apalutamide	22.7 months	20.5 months
TITAN OLE	Apalutamide	44.0 months	39.3 months

Abbreviations: ADT, androgen deprivation therapy; HSPC, hormone-sensitive prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; OLE, open-label extension.

5.2.7. Adverse events in the trials

The EAG extracted Grade 3+ adverse events (AEs) experienced by at least 5% of people in one arm of a trial for use in the economic analysis. The longest timepoint reported in the trials are

presented in Table 11. Hypertension was experienced by at least 5% of people in each of the intervention arm. It was experienced by a substantially higher proportion of people in the abiraterone arm (20.9%) and higher proportion comparator arm (9.8%) in LATITUDE. The EAG understood the high-risk population contributed to this difference. Other AEs that were higher in the abiraterone arms were hypokalaemia and increased alanine aminotransferase (ALT). The EAG's experts stated that increased episodes of hypokalaemia compared to enzalutamide or apalutamide would be expected owing to abiraterone's mechanism of action. However, it is rarely unmanageable and is in part due to the lower prednisolone dose given in the hormone sensitive setting. It is normally relatively simple to manage by increasing the prednisolone dose. ALT rises were also expected to be more common in people treated with abiraterone than with enzalutamide or apalutamide, but are often not symptomatic. There were also some noticeable differences between the AEs reported in the two abiraterone trials (LATITUDE and STAMPEDE). For example, hot flushes and erectile dysfunction. The EAG understood this to be reporting related. The EAG's experts were not concerned about this discrepancy. In sum, abiraterone did appear to result in a higher adverse events burden than enzalutamide or apalutamide but the EAG's expert advice was that they were treatable and did not commonly lead to treatment discontinuation.

Table 11: Grade 3 and above adverse events experienced by at least 5% of people in a treatment arm

	ARCHES-OLE		**LATITUDE-OLE**		**STAMPEDE**		**TITAN**		**TITAN-OLE**	
	All people. Median follow-up: 44.6 months		HR people. Median follow-up 51.8 months		All people. Median follow-up 96 months		All people. Median follow-up 14.4 months		All people. Median follow-up 44 months	
	Enza+ ADT (n=572)	PBO+ ADT (n=574)	Abi+ADT (n=597)	PBO+ ADT (n=602)	Abi+ADT (n=498)	ADT alone (n=502)	Apa+ ADT (n=524)	PBO+ ADT (n=527)	Apa+ ADT (n=524)	PBO+ ADT (n=527)
Hypertension	29 (5.1%)	13 (2.3%)	125 (20.9%)	59 (9.8%)	26 (5.2%)	6 (1.2%)	44 (8.4%)	48 (9.1%)	NR	NR
Hypokalaemia	NR	NR	70 (11.7%)	10 (1.7%)	7 (1.4%)	1 (0.2%)	1 (0.2%)	0	NR	NR
ALT increased	NR	NR	34 (5.7%)	8 (1.3%)	27 (5.4%)	4 (0.8%)	0	1 (0.2%)	NR	NR
Hyperglycaemia	NR	NR	31 (5.2%)	22 (3.7%)	NR	NR	NR	NR	NR	NR
Musculoskeletal events	14 (2.4%)	17 (3.0%)	NR	NR	30 (6.0%)	12 (2.4%)	NR	NR	NR	NR
Erectile dysfunction	NR	NR	2 (0.3%)	0	63 (12.7%)	59 (11.8%)	NR	NR	NR	NR
Hot flashes/flushes	2 (0.3%)	0	0	0	25 (5.0%)	20 (4.0%)	1 (0.2%)	0	NR	NR
Skin rash	0	0	0	0	2 (0.4%)	0	11 (2.1%)	1 (0.2%)	33 (6.3%)	5 (0.9%)

Abbreviations: Abi+ADT, abiraterone with ADT; ADT, androgen deprivation therapy; ALT, Alanine aminotransferase; apa+ADT, apalutamide with ADT; Enza+ADT, enzalutamide with ADT; OLE, open-label extension; PBO+ADT, placebo with ADT.

5.3. Results from the indirect comparisons

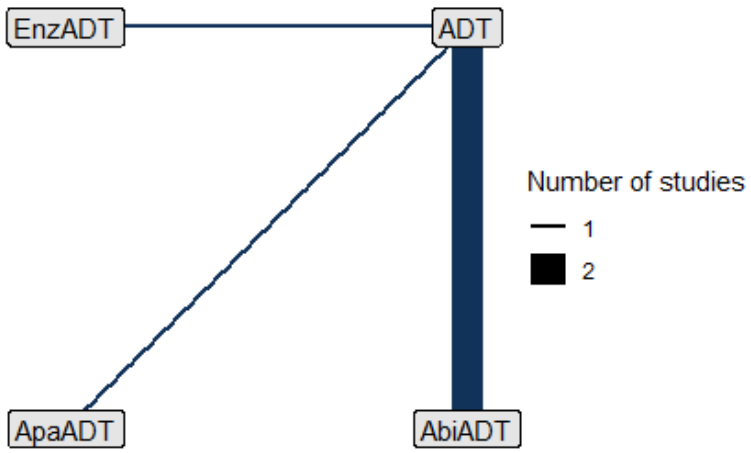
The full treatment network plot is presented in Figure 1. Where data were available the full network was used in the NMAs. However, due to a lack of trial data for some outcomes, it was necessary to use a smaller network with fewer trials. The EAG have referred to American Society of Clinical Oncology (ASCO) Cancer Research Committee guidance on defining clinically meaningful outcomes in their interpretation of the results.[1]

All the results summarised in the main report are based on assuming that treatments effects were fixed rather than random. It should be noted that it is impossible to estimate the variance of a random treatment effect (tau-squared) when fitting an NMA model if there are no closed loops in the treatment network graph and not more than one trial on each of the edges of the graph. In some analyses that were performed, this was the case, and for other analyses, there was one trial on two of the three edges of the graph and two trials on the remaining edge, which resulted in highly imprecise estimates of tau-squared due to there being only one degree of freedom available for its estimation.

The fact that tau-squared could not be precisely estimated, of course, does not mean that it is a variable that should not be taken into account when interpreting the results of the fixed effect NMAs that are about to be presented. Nevertheless, the models associated with these NMAs fitted the data adequately in most cases with no statistically significant departures from the assumption of no heterogeneity between trials in most cases.

The results of sensitivity analyses that supplement the results of the main network meta-analyses that follow are presented in Appendix F, along with additional information concerning these main analyses.

Figure 1: Full network plot



Abbreviations: ADT, ADT alone; EnzADT, enzalutamide with ADT; ApaADT, apalutamide with ADT; AbiADT, abiraterone with ADT.
Notes: ARCHES (EnzADT versus ADT), LATITUDE (AbiADT versus ADT), STAMPEDE (AbiADT versus ADT), TITAN (ApaADT versus ADT)

5.3.1. rPFS

5.3.1.1. Analysis of latest trial data up to a 40 month follow-up

The trials and patient sub-groups included in the analysis are presented below in Table 12. The NMA used the full network and, as previously mentioned in Section 5.2.1.1, the data were taken prior to treatment crossover in the OLEs. Three of the trials provided data in people with high-risk mHSPC with the fourth in people with mHSPC who had a tumour with a Gleason score of eight or more (a high-risk criterion). As noted in Table 6, the outcome for the STAMPEDE trial was PFS based on a clinical definition of this type of survival rather than rPFS, but the results of the two abiraterone trials were consistent.

The median follow-up in the trials varied quite widely and the EAG want to draw attention to the short median follow-up in ARCHES. It was 14.4 months, more than eight months shorter than TITAN, 16 months shorter than LATITUDE, and 25.1 months shorter than STAMPEDE. Kang et al. (2025) assessed the maturity of survival data used in economic models within NICE Single Technology Appraisals (STAs) published between 1st January 2011 to 31st December 2023 (n=301) and categorized survival data according to whether they were: 'highly immature' (<20%

of events), 'immature' (20% - 50%) or 'mature' (>50%).[31] A conclusion of the paper was that the use of immature survival data is one of the main uncertainties and challenges in providing reliable cost-effectiveness evidence in cancer drug appraisals by the National Institute for Health and Care Excellence (NICE).

Most of the trial data were immature (less than fifty percent of people experiencing the event) but the data from ARCHES were highly immature with fewer than 20% having experienced the outcome in the enzalutamide with ADT arm. Given the immaturity of the ARCHES rPFS data, the EAG did not consider results of the NMA relating to enzalutamide with ADT to be robust to extrapolation over substantially longer time periods.

Table 12: Studies and populations included in the rPFS analysis up to 40 months

Study	Intervention	Population	Median follow-up	No. of events (% of patients)		Risk of bias
				Intervention	Control	
LATITUDE	Abi+ADT	High Risk	30.4 mths	239 (40%)	354 (59%)	Low
STAMPEDE	Abi+ADT	High Risk	40.0 mths	198 (21%)	379 (39%)	High
TITAN	Apa+ADT	GS ≥ 8	22.7 mths	167 (31.8%)	277 (52.5%)	Low
ARCHES	Enz+ADT	High Risk	14.4 mths	91 (15.9%)	201 (34.9%)	SC

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide; GS, Gleason Score; mths, months; SC, some concerns

The results of an NMA analysis of rPFS are detailed in Table 13. The NMA demonstrated all three ARPIs with ADT had a statistically significant benefit over ADT alone. The comparisons of ARPIs found abiraterone with ADT to be similarly effective to apalutamide with ADT (HR: 0.97; 95% CrI: 0.73, 1.29). In contrast, the NMA found enzalutamide with ADT to have a numerical benefit over both abiraterone with ADT (HR: 0.73; 95% CrI: 0.51,1.03) and apalutamide with ADT (HR: 0.71; 95% CrI: 0.47, 1.06). The point estimates indicated a strong benefit for enzalutamide despite the credible intervals crossing the line of no effect. However, as noted above, given the high immaturity of the data taken from ARCHES, the EAG did not consider the results relating to enzalutamide with ADT to be robust and considers the results to be substantially more uncertain than indicated by the credible intervals when extrapolating to substantially longer time periods. In sum, given the parity of the NMA results for the abiraterone

with ADT versus apalutamide with ADT comparison, the EAG concluded that both treatments had a similarity of effect for rPFS. In contrast, the results of the NMA did not find abiraterone versus enzalutamide to show a parity of effect, but given the immaturity of the data from the enzalutamide with ADT trial, the EAG considered the results of the NMA too uncertain to draw any conclusions on the similarity or dissimilarity of effect.

These results are broadly similar to the results for rPFS reported in recently published NMAs of the same treatment comparisons in similar patient subgroups that were identified by the systematic literature search described in Section 4. These previously published results can be found in Appendix G. Sensitivity analysis conducted in the mHSPC population found similar results to the primary analysis (Table 62).

Table 13: Estimates of HR for rPFS with 95% credible intervals

	Abi + ADT	**Enz + ADT**	**Apa + ADT**	**ADT**
Abi + ADT	-	1.37 (0.97, 1.94)	0.97 (0.73, 1.29)	0.47 (0.41, 0.54)
Enz + ADT	0.73 (0.51,1.03)	-	0.71 (0.47, 1.06)	0.34 (0.25, 0.46)
Apa + ADT	1.03 (0.77, 1.37)	1.41 (0.94, 2.12)	-	0.48 (0.37, 0.61)
ADT	2.14 (1.86, 2.47)	2.94 (2.15, 4.03)	2.08 (1.63, 2.67)	-

Statistical method: Fixed effect network meta-analysis under the assumption of proportional hazard functions. Cochran's Q statistic for heterogeneity: 0.02 (p=0.90). Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide.

Note: The comparison is the row-forming treatment against the column-forming treatment.

5.3.1.2. Analysis of latest trial data after unblinding

There were insufficient data to complete an NMA for rPFS at the longer timepoints. rPFS was not reported in the LATITUDE OLE, TITAN OLE or at 96 months in STAMPEDE.

5.3.2. OS

The EAG have referred to American Society of Clinical Oncology (ASCO) Cancer Research Committee guidance on defining clinically meaningful outcomes in their interpretation of the results.[1] The Cancer Research Committee selected OS as the primary clinical end point of interest and identified a hazard ratio of 0.8 or less corresponding to an improvement in median OS within a range of 2.5 to 6 months, as the minimum incremental improvement over standard

therapy that would define a clinically meaningful outcome. The EAG have used a hazard ratio of 0.8 or less to delineate a minimum incremental improvement when interpreting OS in this report.

5.3.2.1. Analysis of latest trial data up to a 40-month follow-up

The trials and patient sub-groups included in the analysis are presented in Table 14. The NMA was based on the full network graph and the analysis used the latest trial data up to a 40-month follow-up. Two of the trials provided data for people with high-risk mHSPC, one for people with mHSPC who had a tumour with a Gleason score of eight or more (a high-risk criterion) and one for all people with mHSPC.

The median follow-up in the trials varied quite widely and the EAG again want to draw attention to the short median follow-up in ARCHES which was only 14.4 months. All of the trial data were immature (less than fifty percent of people experiencing the event) but the data from ARCHES were highly immature with fewer than 10% experiencing the outcome in the enzalutamide with ADT arm. Given the immaturity of the ARCHES rPFS data, the EAG did not consider results of the NMA relating to enzalutamide with ADT to be robust to extrapolation to follow-up periods of principal interest, i.e. two years or more.

Table 14: Studies and populations included in the OS analysis up to 40 months

Study	Intervention	Population	Median follow-up	No. of events (% of patients)		Risk of bias
				Intervention	Control	
LATITUDE	Abi+ADT	High Risk	30.4 mths	169 (28%)	237 (39%)	Low
STAMPEDE	Abi+ADT	High Risk	40.0 mths	184 (19%)	262 (27%)	SC
TITAN	Apa+ADT	GS ≥ 8	22.7 mths	83 (16%)	117 (22%)	Low
ARCHES	Enz+ADT	All patients	14.4 mths	39 (6.7%)	45 (7.8%)	Low

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide; GS, Gleason Score; mths, months; SC, some concerns

The results of the NMA analysis of OS are detailed in Table 15. The NMA demonstrated that only abiraterone with ADT had a statistically significant benefit over ADT alone. In interpreting the point estimates using the ASCO guidelines[1] (5.3.2), abiraterone with ADT was found to be similarly effective to apalutamide with ADT (HR: 0.85; 95% CrI: 0.60, 1.22) and to have a clinically meaningful benefit over enzalutamide with ADT (HR: 0.77; 95% CrI: 0.49, 1.21). The EAG cautions that the 95% credible intervals crossed well over the line of no effect in both cases. However, as noted above, given the high immaturity of the data taken from ARCHES, the EAG did not consider the results relating to enzalutamide with ADT to be robust to

extrapolation to periods of time that were longer than the median follow-up time of 14.4 months in the ARCHES trial.

In sum, interpretation of the point estimates using the ASCO guidelines[1] finds abiraterone with ADT to be similarly effect compared to apalutamide with ADT and to have a clinically meaningful benefit over enzalutamide with ADT. However, both point estimates crossed the line of no effect and the enzalutamide OS data from ARCHES was highly immature. Sensitivity analysis conducted in the mHSPC population found similar results to the primary analysis (Table 67).

Table 15: Estimates of HR for OS with 95% credible intervals:

	Abi + ADT	**Enz + ADT**	**Apa + ADT**	**ADT**
Abi + ADT	-	0.77 (0.49, 1.21)	0.85 (0.60, 1.22)	0.62 (0.54, 0.72)
Enz + ADT	1.30 (0.83, 2.05)	-	1.11 (0.65, 1.91)	0.81 (0.53, 1.24)
Apa + ADT	1.17 (0.82, 1.67)	0.90 (0.52, 1.54)	-	0.73 (0.52,1.01)
ADT	1.60 (1.39, 1.85)	1.23 (0.80, 1.90)	1.37 (0.99, 1.91)	-

Statistical method: Fixed effect network meta-analysis under the assumption of proportional hazard functions. Cochran's Q statistic for heterogeneity: 1.56 (p=0.21). Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

5.3.2.2. Analysis of latest trial data after unblinding

The trials and subgroups included in the analysis are presented in Table 16. The NMA was based on the full network graph and the analysis used the latest trial data after the trials became open-label. Two of the trials provided data for people with high-risk mHSPC, one for people with mHSPC who had a tumour with a Gleason score of eight or more (a high-risk criterion) and one for people with mHSPC. The median follow-up in all the trials was greater than 3.5 years and so there were fewer concerns about data maturity for this analysis. By this point, three trials permitted crossover from the comparator treatment to the intervention (Table 7):

- LATITUDE (abiraterone): 12.0%
- STAMPEDE (abiraterone): 0% (not permitted)
- ARCHES (enzalutamide): 31.3%
- TITAN (apalutamide): 39.5%

The increased crossover in the enzalutamide and apalutamide biased the results in favour of abiraterone. However, it was not clear to the EAG how great an influence this had on the results of the NMA. The EAG noted that while there was no crossover in STAMPEDE and the results being from the wider mHSPC population, the OS trial results were very similar to LATITUDE: (STAMPEDE: HR: 0.62; 95% CrI: 0.53, 0.73; LATITUDE: HR: 0.66; 95% CrI: 0.56, 0.78).

Table 16: Studies and populations included in the OS analysis using latest trial data

Study	Intervention	Population	Median follow-up	No. of events (% of patients)		Risk of bias
				Intervention	Control	
LATITUDE	Abi+ADT	High	51.8 mths	275 (46.1%)	343 (57.0%)	High
STAMPEDE	Abi+ADT	All patients	96.0 mths	290 (57.9%)	370 (73.7%)	SC
TITAN	Apa+ADT	High	44.0 mths	112 (38.8%)	160 (55.9%)	High
ARCHES	Enz+ADT	GS≥8	44.6 mths	108 (28.0%)	145 (38.9%)	High

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide; GS, Gleason Score; mths, months; SC, some concerns

The results of the NMA analysis of OS using the latest trial data are detailed in Table 17. The NMA demonstrated all three ARPIs with ADT had a statistically significant benefit over ADT alone. While the point estimates indicated a very small benefit for the comparators, when using the interpretation of clinical efficacy in the ASCO guidelines[1] (Section 5.3.2), abiraterone with ADT was similarly effective to apalutamide with ADT (HR: 1.12; 95% CrI: 0.86, 1.46) and to enzalutamide with ADT (HR: 1.05; 95% CrI: 0.79, 1.38).

In sum, given the parity of the NMA results when comparing abiraterone with ADT, apalutamide with ADT and enzalutamide with ADT, the EAG concluded that these three ARPIs had a similarity of effect for OS. The EAG cautions that the 95% credible intervals crossed well over the line of no effect in all cases and, as noted above, a higher proportion of people in the apalutamide and enzalutamide comparator arms crossed over to the intervention in the OLE biasing the results in favour of abiraterone.

These results, and the results of the NMA outlined in Section 5.3.2.1 for analysis prior to crossover, are broadly similar to the results for OS reported in recently published NMAs of the same treatment comparisons in similar patient subgroups that were identified by the systematic literature search described in Section 4. These previously published results can be found in Appendix G. Sensitivity analysis conducted in the mHSPC population found similar results to the primary analysis (Table 70).

Table 17: Estimates of HR for OS with 95% credible intervals:

	Abi + ADT	Enz + ADT	Apa + ADT	ADT
Abi + ADT	-	1.05 (0.79, 1.38)	1.12 (0.86, 1.46)	0.64 (0.57, 0.72)
Enz + ADT	0.96 (0.73, 1.26)	-	1.07 (0.75, 1.52)	0.61 (0.48 0.78)
Apa + ADT	0.89 (0.69, 1.17)	0.93 (0.66, 1.33)	-	0.57 (0.45 0.73)
ADT	1.57 (1.39, 1.76)	1.64 (1.27, 2.10)	1.57 (1.39, 1.76)	-

Statistical method: Fixed effect network meta-analysis under the assumption of proportional hazard functions. Cochran's Q statistic for heterogeneity: 0.28 (p=0.59). Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide
Note: The comparison is the row-forming treatment against the column-forming treatment.

5.3.3. HRQoL

5.3.3.1. Analysis of latest trial data up to a 40-month follow-up

The only health-related quality of life data that were published for the trials of interest and that could form the basis of a useful comparison between treatments were hazard ratios for the time to deterioration of quality of life (QoL) where the deterioration of QoL was defined as a decrease of ≥10 points in the total Functional Assessment of Cancer Therapy–Prostate (FACT-P) score from baseline. These data were only available for the LATITUDE and ARCHES trials. More specifically, the latest trial data up to a 40-month follow-up was used in this analysis.
Details about the trials and patient sub-groups concerned are presented below in Table 18. One of the trials provided data for people with high risk mHSPC and the other for all people with mHSPC. Again, the median follow-up for ARCHES was 14.4 months and for this reason, the EAG did not consider results of the NMA relating to enzalutamide with ADT to be robust to extrapolation to follow-up periods of principal interest, i.e. two years or more.

Table 18: Studies and populations included in the HRQoL analysis up to 40 months

Trial	Intervention	Population	Median follow-up	No. of events (% of patients)		Risk of bias
				Intervention	Control	
LATITUDE	Abi+ADT	High risk	30.4 mths	347 (58.1%)	369 (61.3%)	Low
ARCHES	Enz+ADT	All patients	14.4 mths	NR	NR	Low

Abbreviations: ADT, Androgen deprivation therapy; Abi, Abiraterone and prednisolone; Enz, Enzalutamide; GS, Gleason Score; mths, months; NR, not reported.

The results of the NMA analysis of time to deterioration are detailed in Table 19. The NMA demonstrated that neither abiraterone with ADT nor enzalutamide with ADT had a statistically

significant benefit over ADT alone. The comparisons of ARPIs found abiraterone with ADT to have a similar effect on QoL to enzalutamide with ADT (HR: 0.89; 95% CrI: 0.71, 1.11).

In summary, given the parity of the NMA results when comparing abiraterone with ADT and enzalutamide with ADT, the EAG concluded that these two ARPIs would appear to have some similarity of effect on time to deterioration of QoL, but given the immaturity of the data from the enzalutamide with ADT trial, the EAG considered the results of the NMA too uncertain to draw any definite conclusions on the similarity or dissimilarity of effect for follow-up periods of principal interest, i.e. two years or more.

Table 17: Estimates of HR for time to deterioration of HRQoL with 95% credible intervals

	Abi + ADT	**Enz + ADT**	**ADT**
Abi + ADT	-	0.89 (0.71, 1.11)	0.85 (0.73, 0.98)
Enz + ADT	1.13 (0.90, 1.41)	-	0.96 (0.81, 1.14)
ADT	1.18 (1.02, 1.36)	1.04 (0.88, 1.24)	-

Statistical method: Fixed effect network meta-analysis under the assumption of proportional hazard functions. Deterioration of QoL was defined as a decrease of ≥10 points in the total Functional Assessment of Cancer Therapy–Prostate score from baseline. Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

5.3.3.2. Analysis of latest trial data after unblinding

There were insufficient data to complete an NMA for HRQoL at the longer timepoints. It was not reported by any of the trials.

5.3.4. Grade 3 or 4 adverse events

5.3.4.1. Analysis of latest trial data up to a 40-month follow-up

The trials and subgroups included in the analysis are presented in Table 19. The NMA was based on the full network graph and the analysis used the latest trial data up to a 40-month follow-up. Data was provided for people with high-risk mHSPC in LATITUDE and the wider mHSPC population in the other three trials.

Table 19: Studies and populations included in the Grade 3 or 4 adverse events analysis up to 40 months

Study	Intervention	Population	Median follow-up	No. of events (% of patients)		Risk of bias
				Intervention	Control	
LATITUDE	Abi+ADT	High risk	30.4 mths	374 (62.6%)	287 (47.7%)	Low
STAMPEDE	Abi+ADT	All patients	40.0 mths	443 (46.7%)	315 (32.8%)	SC
TITAN	Apa+ADT	All patients	22.7 mths	221 (42.2%)	215 (40.8%)	Low
ARCHES	Enz+ADT	All patients	14.4 mths	139 (24.3%)	147 (25.6%)	Low

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide; GS, Gleason Score; mths, months; SC, some concerns

The results of the NMA analysis of Grade 3 or 4 adverse events are detailed in Table 20. The NMA demonstrated that the use of abiraterone with ADT led to a statistically significant increase in Grade 3 or 4 adverse events compared to the use of ADT alone (OR: 1.81; 95% CrI: 1.57, 2.09), apalutamide with ADT (OR: 1.71; 95% CrI: 1.29, 2.27), and enzalutamide with ADT (OR: 1.95; 95% CrI: 1.44, 2.63). The results of the NMA led the EAG to conclude that the use of abiraterone with ADT causes more Grade 3 or 4 events than the use of either ADT alone, enzalutamide with ADT or apalutamide with ADT. Sensitivity analysis conducted in the mHSPC population found similar results to the primary analysis (Table 78).

Table 20: Estimates of OR for a Grade 3 or 4 adverse event with 95% credible intervals

	Abi + ADT	Enz + ADT	Apa + ADT	ADT
Abi + ADT	-	1.95 (1.44, 2.63)	1.71 (1.29, 2.27)	1.81 (1.57, 2.09)
Enz + ADT	0.51 (0.38, 0.70)	-	0.88 (0.61, 1.27)	0.93 (0.71, 1.22)
Apa + ADT	0.58 (0.44, 0.78)	1.14 (0.79, 1.63)	-	1.06 (0.83, 1.35)
ADT	0.55 (0.48, 0.64)	1.07 (0.82, 1.40)	0.94 (0.74, 1.20)	-

Statistical method: Fixed effect network meta-analysis. Cochran's Q statistic for heterogeneity: 0.03 (p=0.8711)
Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide
Note: The comparison is the row-forming treatment against the column-forming treatment.

5.3.4.2. Analysis of latest trial data after unblinding

The trials and subgroups included in the analysis are presented in Table 21. The NMA was based on the full network graph and the analysis used the latest trial data after the trials became open label. Data was provided for people with high-risk mHSPC in LATITUDE and all people with mHSPC in the three other trials.

Table 21: Studies and populations included in the Grade 3 or 4 adverse events analysis using latest trial data

Study	Intervention	Population	Median follow-up	No. of events (% of patients)		Risk of bias
				Intervention	Control	
LATITUDE	Abi+ADT	High risk	51.8 mths	403 (67.5%)	299 (49.7%)	High
STAMPEDE	Abi+ADT	All patients	96.0 mths	271 (54.4%)	192 (38.2%)	SC
TITAN	Apa+ADT	All patients	44.0 mths	259 (49.4%)	220 (41.7%)	High
ARCHES	Enz+ADT	All patients	44.6 mths	224 (39.2%)	160 (27.9%)	High

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide; GS, Gleason Score; mths, months; SC, some concerns

The results of the NMA analysis of Grade 3 or 4 adverse events are detailed in Table 22. The NMA demonstrated that the use of any one of the three ARPIs with ADT led to a substantially greater number of grade 3 or 4 adverse events than the use of ADT alone and the differences concerned were statistically significant. The comparisons of ARPIs found abiraterone with ADT to cause a substantially greater number of Grade 3 or 4 adverse events than the use of apalutamide with ADT and the difference concerned was statistically significant (OR: 1.48; 95% CrI: 1.10, 2.20). While no statistically significant difference was found in the number of Grade 3 or 4 adverse events between the use of abiraterone with ADT and the use of enzalutamide with ADT (OR: 1.22; 95% CrI: 0.90, 1.65) and between the use of enzalutamide with ADT and the use of apalutamide with ADT (OR: 1.22; 95% CrI: 0.86, 1.72), it was probable that abiraterone with ADT caused more Grade 3 or 4 adverse events than enzalutamide with ADT and that enzalutamide with ADT caused more Grade 3 or 4 adverse events than apalutamide with ADT.

In summary, the results of the NMA led the EAG to conclude that the use of abiraterone with ADT causes substantially more Grade 3 or 4 adverse events than the use of ADT alone and apalutamide with ADT and that it is probable that it causes more Grade 3 or 4 adverse events than the use of enzalutamide with ADT. Sensitivity analysis conducted in the mHSPC population found similar results to the primary analysis (Table 80).

Table 22: Estimates of OR for a Grade 3 or 4 adverse event with 95% credible intervals

	Abi + ADT	Enz + ADT	Apa + ADT	ADT
Abi + ADT	-	1.22 (0.90, 1.65)	1.48 (1.10, 2.00)	2.02 (1.71, 2.40)

	Abi + ADT	Enz + ADT	Apa + ADT	ADT
Enz + ADT	0.82 (0.61, 1.11)	-	1.22 (0.86, 1.72)	1.66 (1.30, 2.14)
Apa + ADT	0.67 (0.50, 0.91)	0.82 (0.58, 1.17)	-	1.37 (1.07, 1.74)
ADT	0.49 (0.42, 0.59)	0.60 (0.47, 0.77)	0.73 (0.57, 0.94)	-

Statistical method: Fixed effect network meta-analysis. Cochran's Q statistic for heterogeneity: 0.25 (p=0.62)
Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide.
Note: The comparison is the row-forming treatment against the column-forming treatment.

5.3.5. Fatigue

5.3.5.1. Analysis of latest trial data up to a 40-month follow-up

The trials and subgroups included in the analysis are presented in Table 23. The NMA was based on the full network graph and the analysis used the latest trial data up to a 40-month follow-up. Data was provided for people with high-risk mHSPC in LATITUDE and all people with mHSPC in the three other trials.

Table 23: Studies and populations included in the fatigue (all grades) analysis up to 40 months

Study	Intervention	Population	Median follow-up	No. of events (% of patients)		Risk of bias
				Intervention	Control	
LATITUDE	Abi+ADT	High risk	30.4 mths	77 (12.9%)	86 (14.3%)	Low
STAMPEDE	Abi+ADT	All patients	40.0 mths	648 (68.4%)	551 (57.4%)	High
TITAN	Apa+ADT	All patients	22.7 mths	103 (19.7%)	88 (16.7%)	Low
ARCHES	Enz+ADT	All patients	14.4 mths	138 (24.1%)	112 (19.5%)	Low

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide; GS, Gleason Score; mths, months; SC, some concerns.

The results of the NMA analysis of any reported fatigue are detailed in Table 24. These results show that, compared to the use of ADT alone, the use of abiraterone with ADT led to a statistically significant increase in fatigue. In comparison to the other ARPIs, abiraterone led to similar fatigue with the point estimates slightly favouring enzalutamide and apalutamide. However, the conference intervals were wide and the true relative effect was uncertain. Finally, it should be remarked that the results clearly demonstrate that the measurement of reported fatigue in the STAMPEDE trial was very different from the other three trials and that the degree of heterogeneity between the ORs for LATITUDE and STAMPEDE, i.e. the two trials that tested the use of abiraterone, was statistically significant (p=0.002).

In sum, the results of the NMA led the EAG to conclude that the lack of data and the doubtful quality of available data means that it is difficult to draw any definite conclusions about whether the use of abiraterone with ADT leads to a similar or dissimilar frequency of reported fatigue to the use of ADT alone, enzalutamide with ADT and apalutamide with ADT.
Sensitivity analysis conducted in the mHSPC population (excluding LATITUDE) found quite different results compared to the primary analysis (Table 85). This was due to the measurement of reported fatigue in the STAMPEDE trial was very different from the other three trials and the analysis without LATITUDE meant the abiraterone data came purely from STAMPEDE. The heterogenous results between the main analysis and sensitivity analysis support the EAG's reasoning that it is difficult to draw any definite conclusions from these data.

Table 24: Estimates of OR for fatigue (all grades) with 95% credible intervals

	Abi + ADT	**Enz + ADT**	**Apa + ADT**	**ADT**
Abi + ADT	-	1.06 (0.76, 1.47)	1.14 (0.80, 1.62)	1.39 (1.18, 1.64)
Enz + ADT	0.95 (0.68, 1.31)	-	1.07 (0.70, 1.64)	1.31 (0.99, 1.75)
Apa + ADT	0.88 (0.62, 1.25)	0.93 (0.61, 1.42)	-	1.22 (0.89, 1.67)
ADT	0.72 (0.61, 0.85)	0.76 (0.57, 1.01)	0.82 (0.60, 1.12)	-

Statistical method: Fixed effect network meta-analysis. Cochran's Q statistic for heterogeneity: 9.27 (p=0.002)
Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide
Note: The comparison is the row-forming treatment against the column-forming treatment.

5.3.5.2. Analysis of latest trial data after unblinding

The trials and patient sub-groups included in the analysis are presented in Table 25. The NMA was based on the full network graph and the analysis used the latest trial data after the trials became open label. Data was provided for people with high-risk mHSPC in LATITUDE and all people with mHSPC in the three other trials.

Table 25: Studies and populations included in the fatigue (all grades) analysis using latest trial data

Study	**Intervention**	**Population**	**Median follow-up**	**No. of events (% of patients)**		**Risk of bias**
				Intervention	Control	
LATITUDE	Abi+ADT	High risk	51.8 mths	84 (14.0%)	90 (15.0%)	High
STAMPEDE	Abi+ADT	All patients	96.0 mths	342 (68.7%)	272 (54.2%)	SC
TITAN	Apa+ADT	All patients	44.0 mths	107 (20.4%)	89 (16.9%)	High

Study	Intervention	Population	Median follow-up	No. of events (% of patients)		Risk of bias
				Intervention	Control	
ARCHES	Enz+ADT	All patients	44.6 mths	184 (32.2%)	118 (20.6%)	High

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide; GS, Gleason Score; mths, months; SC, some concerns

The results of the NMA analysis of any reported fatigue are detailed in Table 26. The NMA demonstrated that the use of either abiraterone with ADT or enzalutamide with ADT leads to a statistically significant increase in the incidence of reported fatigue compared to the use of ADT alone. However, while the use of apalutamide with ADT led to a numerical increase in the incidence of reported fatigue compared to the use of ADT alone. In the comparison of ARPIs use of abiraterone with ADT led to a numerical reduction in fatigue versus enzalutamide with ADT. Fatigue was similar between abiraterone and apalutamide, the point estimated favoured apalutamide but the credible intervals were wide. Finally, it should again be remarked that the results clearly demonstrated that the measurement of reported fatigue in the STAMPEDE trial was very different from the other three trials and that the degree of heterogeneity between the ORs for LATITUDE and STAMPEDE, i.e. the two trials that tested the use of abiraterone, was again statistically significant (p=0.001).

In summary, although the results of the NMA appear to indicate that the use of abiraterone may lead to a lower incidence of reported fatigue compared to the use of enzalutamide, the EAG concluded that the lack of data and the doubtful quality of available data means that it is difficult to draw any definite conclusions about whether the use of abiraterone with ADT leads to a similar or dissimilar incidence of reported fatigue to either the use of enzalutamide with ADT or the use of apalutamide with ADT.

Sensitivity analysis conducted in the mHSPC population (excluding LATITUDE) found some differences in the results compared to the primary analysis (Table 87). This was due to the measurement of reported fatigue in the STAMPEDE trial was very different from the other three trials and the analysis without LATITUDE meant the abiraterone data came purely from STAMPEDE. The heterogenous results between the main analysis and sensitivity analysis support the EAG's reasoning that it is difficult to draw any definite conclusions from these data.

Table 26: Estimates of OR for fatigue (all grades) with 95% credible intervals

	Abi + ADT	Enz + ADT	Apa + ADT	ADT
Abi + ADT	-	0.77 (0.55 1.07)	1.12 (0.77, 1.63)	1.42 (1.16, 1.73)
Enz + ADT	1.29 (0.93, 1.81)	-	1.45 (0.96, 2.20)	1.84 (1.41, 2.40)
Apa + ADT	0.89 (0.61, 1.29)	0.69 (0.45, 1.04)	-	1.26 (0.93, 1.73)
ADT	0.70 (0.58, 0.86)	0.54 (0.42, 0.71)	0.79 (0.58, 1.08)	-

Statistical method: Fixed effect network meta-analysis. Cochran's Q statistic for heterogeneity: 10.70 (p=0.001)

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

5.3.6. Grade ≥ 3 Hypertension

5.3.6.1. Analysis of latest trial data up to a 40-month follow-up

The trials and subgroups included in the analysis are presented in Table 27. The NMA was based on the full network graph and the analysis used the latest trial data up to a 40-month follow-up. Data was provided for people with high-risk mHSPC in LATITUDE and all people with mHSPC in the three other trials.

Table 27: Studies and populations included in the Grade ≥ 3 Hypertension analysis up to 40 months

Study	Intervention	Patient sub-group	Median follow-up	No. of events (% of patients)		Risk of bias
				Intervention	Control	
LATITUDE	Abi+ADT	High risk	30.4 mths	121 (20.3%)	59 (9.8%)	Low
STAMPEDE	Abi+ADT	All patients	40.0 mths	44 (4.6%)	13 (1.4%)	SC
TITAN	Apa+ADT	All patients	22.7 mths	44 (8.4%)	48 (9.1%)	Low
ARCHES	Enz+ADT	All patients	14.4 mths	19 (3.3%)	10 (1.7%)	SC

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide; GS, Gleason Score; mths, months; SC, some concerns

The results of the NMA analysis of Grade ≥ 3 hypertension events are detailed in Table 28. The NMA demonstrated that the use of abiraterone with ADT leads to a substantial increase in the number of Grade ≥ 3 hypertension events compared to the use of ADT alone and the difference concerned was statistically significant (OR: 2.60; 95% CrI: 1.94, 3.49).

The comparisons of ARPIs found abiraterone with ADT to cause a substantially greater number of Grade ≥ 3 hypertension events than the use of apalutamide with ADT and the difference concerned was statistically significant (OR: 2.84; 95% CrI: 1.70, 4.79). On the other hand, the difference in the number of Grade ≥ 3 hypertension events between using abiraterone with ADT and enzalutamide with ADT was not statistically significant and the corresponding 95% credible interval was too wide to draw any definite conclusions about the relative effect of the two ARPIs concerned on the incidence of these events (OR: 1.30; 95% CrI: 0.55, 2.97).

In summary, the results of the NMA led the EAG to conclude that the use of abiraterone with ADT causes a substantially greater number of Grade ≥ 3 hypertension events than the use of apalutamide with ADT but the lack of data meant that it was not possible to draw any definite conclusions about whether there is similarity or dissimilarity in the incidence of Grade ≥ 3 hypertension events between using abiraterone with ADT and using enzalutamide with ADT. Sensitivity analysis conducted in the mHSPC population found similar results to the primary analysis (Table 93).

Table 28: Estimates of OR for grade ≥ 3 hypertension with 95% credible intervals

	Abi + ADT	**Enz + ADT**	**Apa + ADT**	**ADT**
Abi + ADT	-	1.30 (0.55, 2.97)	2.84 (1.70, 4.79)	2.60 (1.94, 3.49)
Enz + ADT	0.77 (0.34, 1.82)	-	2.18 (0.90, 5.48)	1.99 (0.93, 4.48)
Apa + ADT	0.35 (0.21, 0.59)	0.46 (0.18, 1.11)	-	0.91 (0.60, 1.40)
ADT	0.38 (0.29, 0.51)	0.50 (0.22, 1.08)	1.09 (0.71, 1.68)	-

Statistical method: Fixed effect network meta-analysis. Cochran's Q statistic for heterogeneity: 1.32 (p=0.25)

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

5.3.6.2. Analysis of latest trial data after unblinding

The trials and subgroups included in the analysis are presented in Table 29. For the trials included in this analysis, the latest trial data after the trials became open label was used. Since no new data on Grade ≥ 3 hypertension was published after the TITAN trial become open label and the data that was available for this adverse event corresponded to a median follow-up time of 22.7 months which was substantially lower than the median follow-up times for the data that was available for the other three trials after they became open label, this NMA did not include any data on Grade ≥ 3 hypertension from the TITAN trial.

For the included trials, data was provided for people with high-risk mHSPC in LATITUDE and all people with mHSPC in the remaining two trials.

Table 29: Studies and populations included in the Grade ≥ 3 Hypertension analysis using latest trial data

Study	Intervention	Patient sub-group	Median follow-up	No. of events (% of patients)		Risk of bias
				Intervention	Control	
LATITUDE	Abi+ADT	High risk	51.8 mths	125 (21.0%)	60 (10.0%)	High
STAMPEDE	Abi+ADT	All patients	96.0 mths	26 (5.2%)	6 (1.2%)	SC
ARCHES	Enz+ADT	All patients	44.6 mths	29 (5.1%)	13 (2.3%)	High

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide; GS, Gleason Score; mths, months; SC, some concerns

The results of the NMA analysis of Grade ≥ 3 hypertension events are detailed in Table 30. The NMA demonstrated that the use of either abiraterone with ADT or enzalutamide with ADT leads to a substantial increase in the number of Grade ≥ 3 hypertension events compared to the use of ADT alone and the differences concerned are statistically significant. The comparison of the use of abiraterone with ADT and the use of enzalutamide with ADT showed no difference in the impact of these treatments on the number of Grade ≥ 3 hypertension events, but the 95% credible interval concerned was too wide to draw any definite conclusions about this treatment comparison (OR: 1.00; 95% CrI: 0.47, 2.02).

In summary, the results of the NMA led the EAG to conclude that the lack of data meant that it was not possible to draw any definite conclusions about whether there is similarity or dissimilarity in the frequency of Grade ≥ 3 hypertension events between using abiraterone with ADT and using enzalutamide with ADT. Sensitivity analysis conducted in the mHSPC population found similar results but with substantially wider credible intervals in comparison to the primary analysis (Table 95).

Table 30: Estimates of OR for Grade ≥ 3 hypertension with 95% credible intervals

	Abi + ADT	Enz + ADT	ADT
Abi + ADT	-	1.00 (0.47, 2.02)	2.34 (1.85, 2.99)
Enz + ADT	1.00 (0.49, 2.13)	-	2.35 (1.22, 4.81)
ADT	0.43 (0.33, 0.54)	0.43 (0.21, 0.82)	-

Statistical method: Fixed effect network meta-analysis. Cochran's Q statistic for heterogeneity: 2.36 (p=0.12)
Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide
Note: The comparison is the row-forming treatment against the column-forming treatment.

5.4. Conclusions on clinical equivalence

The objective of the clinical SLR conducted for this appraisal was to assess whether abiraterone with ADT is likely to provide similar or greater health benefits than technologies recommended in published NICE technology appraisal guidance for the same indication. The relevant population for this appraisal were people with high-risk mHSPC and the relevant comparators for were enzalutamide with ADT and apalutamide with ADT (Section 2.3).

An NMA was conducted using four RCTs linking each of the interventions via the common comparator ADT alone. The trials were each well conducted but variations in the trials led to concerns related to the risk of bias in the NMA. LATITUDE recruited the population of interest, people with high-risk mHSPC, but the other RCTs recruited more widely; STAMPEDE (HSPC), ARCHES (mHSPC), TITAN (mHSPC). Where possible subgroup analysis presented in the trials were used in the NMAs but in a number of cases this was not possible. In addition, LATITUDE, ARCHES, and TITAN were trials with open-label extensions (OLEs) and this led to large deviations from the intended interventions at the longer timepoints in the trials. The ARCHES trial was notable because its OLE began after a median 14.4 treatment leading to highly immature time to event data in the period before unmasking and treatment crossover. Also, a higher proportion of people in the comparator arms in ARCHES (enzalutamide; 31.3%) and TITAN (apalutamide; 39.5%) crossed over compared to LATITUDE (abiraterone; 12.0%) or STAMPEDE (abiraterone; 0%). Given the OLE structures of three of the RCTs it was appropriate to conduct NMAs prior to any treatment crossovers where data were often immature and at the latest timepoints after treatment crossover where data were more mature but at a high risk of bias.

It was only possible to conduct an NMA for rPFS at the randomised period, prior to any permitted treatment crossover. The NMA used high-risk mHSPC data from three trials, people with mHSPC and a Gleason score eight or more in the fourth. The NMA found abiraterone and apalutamide to be similarly effective but the outcome data for enzalutamide, from ARCHES, was too immature and consequently too uncertain to draw any conclusions on the similarity or dissimilarity of effect. However, recent research in Shore et al. (2025) analysed 31 RCTs in people with mHSPC (including ARCHES, LATITUDE, STAMPEDE, and TITAN) and found rPFS

was a reliable surrogate for OS.[2] Therefore, given the strong evidence of similarity of effect between enzalutamide and abiraterone in OS, it is rational to assume a similarity of effect for rPFS given the absence of strong clinical evidence in either direction. The rPFS results in this report's NMA was broadly similar to the results for rPFS reported in recently published NMAs of the same treatment comparisons in similar mHSPC subgroups (Appendix G).

NMAs were conducted for OS at the randomised period and at the final timepoint after people had been permitted to crossover from comparator to the intervention in the three OLEs. Both NMAs used high-risk mHSPC from two trials, people with mHSPC and a Gleason score eight, in one, and people with mHSPC in the fourth. The NMAs consistently found abiraterone to be non-inferior to the comparators. The OS results were broadly similar to the results for OS reported in recently published NMAs of the same treatment comparisons in similar patient subgroups (Appendix G.).

The smaller HRQoL NMA, time to a decrease of 10 points in FACT-P score from baseline. This NMA used people with high-risk mHPSC from LATITUDE and people with mHSPC from ARCHES, and found no difference between the treatments.

NMAs were also undertaken for safety outcomes and these analyses used people with high-risk mHSPC from LATITUDE and people with mHSPC from the other trials. The NMAs found people on abiraterone had more Grade 3+ AEs than those treated with enzalutamide or apalutamide and more hypertension (Grade 3+) than those treated with apalutamide. It was not possible for the EAG to draw any conclusions related to fatigue (all grades).

In sum, differences between the trials led to NMAs caveated with noted uncertainties linked to immature data and large deviations from the intended interventions at the later timepoints. However, the analysis consistently found abiraterone provided similar or greater health benefits in terms of OS and, immature ARCHES data aside, rPFS. The NMAs did find treatment with abiraterone to result in a higher adverse events burden than enzalutamide or apalutamide. However, in the EAG's clinical expert's experience of using abiraterone in their practice, adverse events were treatable and did not commonly lead to treatment discontinuation.

6. ECONOMIC EVIDENCE SEARCHES AND SELECTION

6.1. Evidence search strategy and study selection

Three targeted reviews were undertaken to identify relevant evidence to inform the appraisal of abiraterone and broader considerations given this is the first pilot of appraisal of a generic treatment where the originator product was not recommended. This three-pronged search rationale is fully described in the published protocol. No amendments to the planned search process were made.

Across all three searches, only English language publications were included, and only those studies in which the healthcare system setting was comparable to the NHS in England.

6.2. Search strategy for previous NICE submissions

Prior NICE appraisals of androgen receptor pathway inhibitors (ARPIs) were identified by iterative searches of the NICE website, using scoped intervention and comparator terms. All relevant articles from the "History" tab of the identified prior appraisals (including the committee papers, final appraisal documents, appraisal consultation documents, and expert submissions) were downloaded and evaluated by the project team.

6.3. Search strategy for previous economic evaluations

Details of the search approach for previous economic evaluations of abiraterone conducted since the NICE appraisal (published 18th August 2021), including lists of databases, search strategies and outcomes, can be found in Appendix A. Screening took place in Rayyan[12] and was performed using the inclusion and exclusion criteria described in the published protocol. A PRISMA diagram of the search and screen process for previous economic evaluations is provided in Figure, Appendix B.

6.4. Search strategy for literature related to assessment of biosimilars and generics

Details of the search approach for recent publications evaluating the cost-effectiveness of the introduction of biosimilars or generics into a clinical pathway, and the methods used for these types of evaluation, can be found in Appendix A. This search – in addition to database screening – also included the trawling of key HTA bodies' websites to identify any relevant methods documentation. Screening took place in Rayyan[12] and was performed using the

inclusion and exclusion criteria described in the published protocol. A PRISMA diagram of the search and screen process for previous economic evaluations is provided in Figure 8, Appendix B.

6.5. Included and excluded studies

None of the previous models identified addressed the NICE decision problem for this appraisal directly.

6.5.1. Review of previous NICE submissions

Four relevant previous NICE submissions were identified. The Excel files for the economic models were provided to the EAG by the NICE team.

- TA903: Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer. Published 21 June 2023
- TA741: Apalutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer. Published 28 October 2021
- TA721: Abiraterone for treating newly diagnosed high risk metastatic hormone naïve prostate cancer. Published 18 August 2021, not recommended
- TA712: Enzalutamide for treating hormone-sensitive metastatic prostate cancer. Published 7 July 2021

None of the appraisals compared any of the treatments within scope for this appraisal. TA903 included enzalutamide as a comparator, apalutamide was removed from the final scope as a comparator as it was only recommended in patients not suitable for docetaxel.

6.5.2. Review of previous economic evaluations

There were 21 economic evaluations that met the inclusion criteria, plus the four previous TAs making a total of 25 publications included for the review. Of those, five were UK based (four previous TAs and Clarke et al, 2022[32]; Table 31). Clarke et al was a 2022 cost utility analysis to evaluate the cost effectiveness of abiraterone in men initiating long-term ADT treatment for prostate cancer based on the STAMPEDE trial.

Table 31: Number of evaluations by setting

Setting	Number of evaluations
USA	8
UK	5
Canada	2
Japan	2
Brazil	1
Sweden	1
Singapore	1
Switzerland	1
Columbia	1
France	1
India	1
Multiple country setting	1

Of the 25 evaluations included, 16 were cost-utility analyses, three were cost-effectiveness analyses, and the other six were a combination of systematic reviews, registry studies, resource utilisation studies and rapid evidence reviews. The majority of evaluations used the healthcare system payers perspective (21 out of 25).

From the UK setting, most of the cost and QALY information from the previous TAs was redacted. Clarke et al. (2022)[32] did report costs and QALYs for abiraterone and ADT monotherapy. The QALYs for abiraterone were 3.79 and the costs were £116,658 based on a daily cost of £94.69 using 2018 BNF prices.

Table 32 provides the evaluations that reported QALY outcomes as part of the evaluation results. 11 of the 25 evaluations reported QALYs for one or more of the interventions and comparators.

[redacted]

[redacted]

Sung 2021 and Wang 2022 were considered the most appropriate evaluations to inform the analysis of QALY outcomes. Both studies used lifetime models and included all of the clinical trials associated with the treatments included in the *de novo* NMA presented in this report (STAMPEDE, LATITUDE, TITAN). Both studies were conducted from a US perspective, appeared to be of reasonable quality, calibrated OS estimates to available observed data and were not sponsored by any of the involved manufacturers. The incremental QALYs for enzalutamide vs ADT in Sung 2021 was 2.85 (83%) and 0.54 (16%) in Wang 2022. [redacted]

[redacted]

The incremental QALYs for apalutamide vs ADT in Sung 2021 was 2.07 (61%) and 1.63 (48%) in Wang 2022. [redacted]

[redacted]

The incremental QALYs for abiraterone vs ADT in Sung 2021 was 1.98 (58%) and 1.38 (41%) in Wang 2022. [redacted].

Table 32: QALY outcomes by treatment

Evaluation	QALYs Abi + ADT	QALYs Apa + ADT	QALYs Enz + ADT	QALYs Doc + ADT	QALYs Dar+Doc	QALYs ADT
Barbier 2022[33]	5.33	4.9	5.15	3.97	NR	3.25
Clarke 2022[32]	3.79	NR	NR	NR	NR	1.65
Naqvi 2024[34a]	High volume: 2.87	High volume: 2.92	NR	High volume: 1.84	NR	High volume: 1.77
TA721[35]	[redacted]	NR	NR	[redacted]	NR	[redacted]
TA741	NR	[redacted]	NR	[redacted]	NR	[redacted]
TA712	NR	NR	[redacted]	[redacted]	NR	[redacted]
TA903	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
Gupta 2024[36]	4.78	3.22	5.03	2.61	NR	NR
Handorf 2023[37]	5.05	NR	NR	4.57	NR	NR
Litvin 2025[38]	NR	6.44	NR	NR	5.64	NR
Yoo 2023[39]	3.83	4.16	4.57	3.79	4.29	3.25
Sathianathen 2024[40]	3.32	3.18	3.71	2.76	3.79	2.59
Sung 2021[41]	5.40	5.49	6.27	3.70	NR	3.42
Wang 2022[42]	4.76	5.01	3.92	3.92	NR	3.38

Abbreviations: Abi, abiraterone; ADT, androgen deprivation therapy; Apa, apalutamide; Enza, enzalutamide; Doc, docetaxel; Dar, darolutamide; NR, not reported; QALYs, quality adjust life years; TA, technology appraisal

Note: cPAS marking indicates data taken from company models from previous appraisals

[a]Navqi 2024[34] is an abstract and does not define high and low volume disease. CHAARTED and GETUF-AFU 15 define high volume as the presence of visceral metastases and/or ≥ four bone metastases with at least one outside of the vertebral column and pelvis Kyriakopoulos et al, 2018.[43]

Litvin 2025[38] and Naqvi 2024[34] stratified patients by their risk profile, either high or low risk in the mHSPC state and reported costs and QALYs by risk stratification.

The relevant costs for monitoring and adverse events that were extracted from the previous TAs and Clarke 2022[32] are presented in section 7.1.2.2 and section 7.1.2.3 respectively as cost parameters used to inform the cost-comparison model.

Table 33 provides a summary of evaluations which compared abiraterone with either apalutamide or enzalutamide. None of these were conducted from a UK perspective.

Table 34 shows the range of incremental QALY gains in evaluations which compared abiraterone to apalutamide was -0.33 to 1.56. Studies were highly inconsistent as to which treatment was expected to demonstrate greater benefit. Table 35 shows the range of incremental QALY gains in evaluations which compared abiraterone to enzalutamide was 0.84 to -0.74. All studies except Barbier 2022[33] (a study by the Swiss Medical Board which uses non-standard methods to estimate comparative effectiveness) and Wang 2022 predicted enzalutamide to be the more effective treatment.

Sung 2021 and Wang 2022 were considered the most appropriate evaluations to inform the QALY gain range required for apalutamide and enzalutamide in order for abiraterone to be no longer cost effective. The upper and lower bounds of the QALY gains required for apalutamide are 0.09 and 0.25. The QALY gains required for enzalutamide are 0 and 0.87.

Table 33: Evaluations that analysed abiraterone, apalutamide and enzalutamide

Evaluation	Setting	Perspective	Sponsor	Risk status	Model structure	Time horizon	Discount rate	Source of effectiveness data
Barbier 2022[33]	Switzerland	Healthcare payer	Swiss medical board	All risk	3-state cohort simulation model Progression-free disease (PF) Progressive disease (PD) Death	30 years	3.00%	OS: STAMPEDE (**Clarke et al. 2019**)[44] OS: STAMPEDE (James et al, 2017[30], M1 subgroup) OS: ARCHES (Armstrong et al, 2019)[15] PFS: STAMPEDE (Clarke et al, 2019)[44] PFS: ARCHES (Armstrong et al. 2019)[15]
Gupta 2024[36]	India	Healthcare payer	Department of Health Research, Ministry of Health and Family Welfare, Government of India	All risk	Multi state model Progression free survival Progressive disease Best supportive care Death	Lifetime	3.00%	Abi PFS: STAMPEDE (James et al, 2017)[30] Enz PFS: ARCHES (**Armstrong et al, 2022**)[14] OS: ARCHES (Armstrong et al, 2021)[45] Apa PFS: TITAN (**Chi et al, 2021**)[22] / (Chi et al, 2019)[21]
Sathianathen 2024[40]	USA	Health sector	NR	All risk	State transition model mHSPC CRPC Death	Lifetime	3.00%	Abi + ADT: STAMPEDE [James et al, 2017][30] Abi+ADT: PEACE-1 (Fizazi et al, 2022[46]) Apa + ADT TITAN [**Chi et al, 2019**][21] Enz + ADT: ENZAMET (Sweeny et al, 2023[47])
Sung 2021[3]	USA	Payer	NR	All risk	State transition model Progression free (mHSPC) Progression (CRPC) Death	Lifetime	3.00%	Abi+ADT: STAMPEDE (James et al, 2017)[30] LATITUDE (Fizazi et al, 2017)[16] Enz+ADT: ARCHES (Armstrong et al, 2019)[15] Apa+ADT: TITAN (Chi et al, 2019)[21]
Wang 2022[42]	USA	Health sector	Ellen B Gold Scholarship and Pharmaceutical Research and	All risk	Partitioned survival model mCSPC	Lifetime	3.00%	Abi+ADT: STAMPEDE [James et al, 2017][30]

Evaluation	Setting	Perspective	Sponsor	Risk status	Model structure	Time horizon	Discount rate	Source of effectiveness data
			Manufacturers of America Foundation 2020 Predoctoral Fellowship in Health Outcomes Research		mCRPC Death.			Abi+ADT: LATITUDE [Fizazi et al, 2017][16] [Chi et al, 2018][48] Apa+ADT: TITAN (**Chi et al, 2019**[21]) (**Agarwal et al, 2019**[49]) Enz+ADT: ARCHES (Armstrong et al, 2019) Enz+ADT: ENZAMET (Davis et al, 2019[50])
Yoo 2023[39]	USA	Public sector	National Cancer Institute/National Center for Advancing Translational Sciences	All risk	Partitioned survival model Progression free Progressive disease to CRPC Death	10 years	3.00%	Abi + ADT: LATITUDE / STAMPEDE / [Fizazi et al, 2017][16] [**Fizazi et al, 2019**][17] Apa + ADT TITAN [Chi et al, 2019][21] Enza + ADT: ENZAMET (Armstrong et al, 2022[14])

Abbreviations: Abi, abiraterone; ADT, androgyn deprivation therapy; Apa, apalutamide; CRPC, castrate resistant prostate cancer; Doc, docetaxel; Daro, darolutamide; Enz, enzalutamide; mCRPC, metastatic castrate resistant prostate cancer; mCSPC, metastatic castrate sensitive prostate cancer; mHSPC, metastatic hormone sensitive prostate cancer; OS, overall survival; PFS, progression free survival

Latest trial data cuts have been noted using bold text in the table.

Notes: ENZAMET was not included in the EAG NMA as it could not be connected to the network without major assumptions the comparator was ADT + standard non-steroidal antiandrogen (bicalutamide, nilutamide or flutamide) and docetaxel was given as required during the trial. PEACE-1 was not included in the EAG NMA as it could not be connected to the network without major assumptions. Participants were randomly assigned (1:1:1:1) to standard of care (androgen deprivation therapy alone or with intravenous docetaxel 75 mg/m^2 once every 3 weeks), standard of care plus radiotherapy, standard of care plus abiraterone (oral 1000 mg abiraterone once daily plus oral 5 mg prednisone twice daily), or standard of care plus radiotherapy plus abiraterone.

Table 34: Incremental costs, QALYs and ICER for abiraterone vs apalutamide

Evaluation	Incremental QALYs	Incremental cost	ICER
Barbier 2022[33]	0.43	-101,611 EUR	Dominant
Gupta 2024[36]	1.56	-6,311,047 INR	Dominant
Sathianathen 2024[40]	0.14	18,384 USD	131,314 USD
Sung 2021[41]	-0.09	-507,382 USD	5,637,578 USD SW quadrant
Wang 2022[42]	-0.25	-494,919 USD	1,979,676 USD SW quadrant
Yoo 2023[39]	-0.33	-436,980 USD	1,324,182 USD SW quadrant

Abbreviations: EUR, euro currency; ICER, incremental cost effectiveness ratio; INR, Indian rupee currency; QALYs, quality adjusted life years; USD, united states dollar currency

Table 35: Incremental costs, QALYs and ICER for abiraterone vs enzalutamide

Evaluation	Incremental QALYs	Incremental cost	ICER
Barbier 2022[33]	0.18	-107,435 EUR	Dominant
Gupta 2024[36]	-0.25	-801,431 INR	3,147,770 INR SW quadrant
Sathianathen 2024[40]	-0.39	-32,255 USD	90,397 USD SW quadrant
Sung 2021[3]	-0.87	-444,529 USD	509,813 USD SW quadrant
Wang 2022[42]	0.84	-132,523 USD	Dominant
Yoo 2023[39]	-0.74	-441,895 USD	597,155 USD SW quadrant

Abbreviations: EUR, euro currency; ICER, incremental cost effectiveness ratio; INR, Indian rupee currency; QALYs, quality adjusted life years; USD, united states dollar currency

6.5.3. Review of literature related to assessment of biosimilars and generics

Available literature on the appraisal of generics or biosimilars for new indications in which the originator product was not recommended were sparse. This is likely in part due to a lack of commercial incentives for this type of analysis.[51]

The NICE manual 2022 specifies that NICE will do surveillance of guidance because of loss of marketing exclusivity when:

the original guidance (including for technologies that are used in combination with other technologies) resulted in the technology being recommended (as an option) in specific circumstances (optimised use), recommended only in research context or not recommended

the biosimilars or generics of the technology are licensed for the same indication

the original economic model can be used for the purpose of the update and consent has been received from the originator company for the model to be used for this purpose.

The EAG is not aware of any instances of this.

The prior assessment conducted by the AWMSG for generic abiraterone was the most relevant study identified.[52] Only a budget impact assessment was conducted. Median treatment durations were compared naively from individual trials and the AWMSG concluded that on the basis of similarity (medians 33 – 40 months) all patients would have approximately 3 years of treatment. Clinical experts indicated 5-10% of patients receiving androgen-receptor targeted treatment would be eligible for abiraterone and based upon data from the Velindre Cancer Centre (which covers ~50% of the population in Wales) that in the absence of abiraterone 40% of patients would receive apalutamide and 60% would receive enzalutamide.

In Canada specific guidance was produced for the assessment of biosimilars in the context of biologics.[53] Canadian policy initial required a full CADTH assessment for biosimilar,[53,54] however, in later years this requirement was removed and instead companies moved straight to price negotiation. The process for this was unclear from the documentation.

In Scotland a full submission was originally required for indication(s)/populations where the reference product is not recommended by SMC/HIS.[55] Since March 2024 this has no longer been the case; not recommended advice for the originator now no longer applies once generic or biosimilar medicines become available and instead decisions are made on inclusion in local / regional formularies separately.

ICER guidelines provide similar guidance to NICE appraisals on accounting for cost variation for generics and biosimilars: their reference case is to use the median cost across all versions with sensitivity analysis using the lowest and highest price.[56] NICE guidelines specify use of the midpoint, lowest and highest prices with sensitivity and scenario analysis using the midpoint.[57]

As noted in Hughes 2019,[54] considerations for biosimilars differ somewhat to generics as generics can be shown to be identical to the reference drug whereas for biosimilars the

manufacturer has to demonstrate that it is unlikely that differences in quality attributes would have an adverse effect on safety or efficacy. There are a small number of studies (such as NOR-SWITCH in Crohn's disease which looked biosimilar vs originator infliximab[58] and the REOLA real-world study for follitropin alfa in fertility treatment[59]) which suggest reduced effectiveness for patients using the biosimilar product. This may in part be attributable to the "nocebo" effect which occurs when there is a loss of effectiveness or presence of adverse events due to a patient's negative expectations of the treatment.[60] However, Hughes's exploration of the cost-effectiveness implications of the small reduction in effectiveness from the NOR-SWITCH study did, however, find this was unlikely to impact on cost-effectiveness conclusions (mean incremental costs -$46,194 vs mean incremental QALYs -0.13) which would be expected to be the case for the majority of biosimilars.

The models identified which looked at the introduction of a new biosimilar into a treatment pathway where the originator product was not recommended[61-63] or which investigated extension of the patient population[64] did not describe any preferred method to account for any potential differences in effectiveness between biosimilar and originator product.

One previous submission looking at biosimilar products in comparison to the originator did account for these types of differences, however, this was not technically within the scope of this review.[65]

The prior assessment conducted by the AWMSG for generic abiraterone was the most relevant study identified.[52]

A key issue with appraisal of biosimilars / generics outside of the current situation, as highlighted in Clarke et al. (2024)[66] and Cornes et al. (2022),[64] is the likelihood of increased coverage with these products compared to reference products. The likelihood of this and the impact of relevant comparators should be assessed on a disease-specific basis. In our case, based upon clinical expert input received, it is unlikely that a significant proportion of patients would not already be receiving treatment in addition to ADT.

Another key issue identified in Clarke et al. (2024)[66] is continuity of supply. Communication from Peter Johnson at NHS England indicated that they did not expect any supply issues for generic abiraterone as the volume of use is expected to be sufficient to make it economically viable.

7. ECONOMIC EVALUATION

7.1. Economic evaluation

7.1.1. Evaluation structure

The primary economic evaluation was performed under a cost comparison framework which assumes similar or greater benefits for similar or lower costs (see Section 5.4). As the assumption of similar effectiveness was deemed to have some uncertainty we produced an assessment of the difference in quality-adjusted life-years (QALYs) that would be required to justify the increased cost of comparator treatments based upon £20,000 and £30,000 per QALY willingness to pay thresholds. This was then critiqued using available literature to determine the plausibility of difference in QALY gains.

The economic evaluation was conducted from the perspective of the NHS and PSS in England and Wales using a time horizon equal to the expected time on treatment of three years. This in line with the median time on treatment ranges from ARCHES-OLE (40.2 months), LATITUDE-OLE (25.8 months), STAMPEDE mHSPC (33.2 months) and TITAN-OLE (39.3 months) (Table 10). A scenario analysis of a two year time horizon was conducted as this is in line with the median time on treatment in the high-risk population in LATITUDE.

In line with the underlying assumption of similar effectiveness a similar duration of treatment was assumed for all interventions.

The model had a 28-day cycle length (in line with the pack sizes for included treatments). Discounting was not included in line with NICE guidance for cost comparison submissions. When we explored the QALYs required to justify increased costs we included discounting, at a rate of 3.5%, for both costs and QALYs, in line with the NICE reference case.

Costs included were acquisition costs, treatment-specific monitoring costs and adverse event costs. Resource use linked to prostate cancer rather than to treatment-specific monitoring was not included because if the treatments are similarly effective this would be expected to be similar. Similarly, the cost of subsequent treatment was not included as it also would be expected to be similar.

7.1.2. Resource use and cost parameters

7.1.2.1. Acquisition costs

Treatment costs (Table 36) were collected from the eMIT national database 2024[67] where available, where unavailable costs were collected from the BNF medicinal forms for the treatment.[68,69] Costs are presented at list price for all treatments. Costs including confidential price discounts are included in the cPAS appendix. ADT costs were not included in the analysis as they are expected to be equal across treatments. Dosage information was collected from the SmPC for each treatment. Data on relative dose intensity was available apalutamide from TITAN (mean 95.76%); [redacted]. Given this an RDI of 100% was assumed for all treatments in the EAG base case and scenario analysis conducted assuming an RDI of 95% for all treatments to test the impact.

Table 36: Acquisition costs

Treatment	Dosage	Cost per pack	Sources	Cost per year
Abiraterone	1,000 mg (two 500 mg tablets) as an oral single daily dose with.	£76.91 per 28 days	Dosing: Abiraterone SmPC[70] Cost: eMIT national database 2024[67]	£1,076.74
Prednisolone	5 mg prednisolone daily*	£0.41 per 14 days	Dosing: Prednisolone SmPC[71] Cost: eMIT national database 2024[67]	£10.66
Abiraterone + prednisolone				£1,087.40
Enzalutamide	160 mg (four 40 mg tablets) as an oral single daily dose	£2,734.67 per 28 days	Dosing: Enzalutamide SmPC[72] Cost: BNF Enzalutamide[68]	£35,550.71
Apalutamide	240 mg (four 60 mg tablets) as an oral single daily dose	£2,735.00 per 28 days	Dosing: Apalutamide SmPC[73] Cost: BNF Apalutamide[69]	£35,555.00

*prednisone is no longer available in the UK

Abbreviations: BNF, British national formulary; eMIT, electronic market information tool; mg, milligrams; RDI, relative dose intensity; smPC, summary of product characteristics

7.1.2.2. Monitoring and administration costs

The only difference in monitoring expected across treatments was the need for additional blood tests and associated oncology visits for abiraterone in the first 3 months of treatment. It was assumed that all 3 treatments require full blood counts and an oncology visit every 4 weeks after the first 3 months with people on abiraterone requiring these every 2 weeks for the first 3 months of treatment (Table 37). This was broadly in line with TA721, clinical expert input to the EAG and monitoring information from the abiraterone SmPC.[70] PSA and testosterone testing, liver and kidney function tests and CT scans were all assumed to be conducted at the same frequency for all 3 treatments and were therefore not included in the model base case.

Administration costs are not included in the analysis as abiraterone, enzalutamide, apalutamide and prednisolone are all taken as oral tablets.

To explore the impact of less frequent long-term monitoring, a scenario analysis was conducted in which the monitoring frequency for enzalutamide and apalutamide was reduced from every 4 weeks to every 6 weeks. This is consistent with the reduced frequency of monitoring assumed in the enzalutamide and apalutamide appraisals and the frequency assumed for enzalutamide in the mCRPC setting in TA721.

Table 37: Monitoring costs

Treatment	Type of monitoring	Unit cost per visit	Frequency of visit	Source	Cost per year
Abiraterone	Full blood count	£3.10	Every 2 weeks for the first 3 months, every 4 weeks post 3 months	Type: SmPC abiraterone[70] / Clinical expert input to EAG Unit cost: NHS Cost Collection 2024[74] national average unit cost clinical biochemistry (PATH04) Frequency: TA721[35] / Clinical expert input to EAG	£45 for year 1, £36 per year for subsequent years
Abiraterone	Oncologist visit	£193.89	Every 2 weeks for the first 3 months, every 4 weeks post 3 months	Type: SmPC Abiraterone[70] / Clinical expert Unit cost: National Schedule of NHS Costs (2023/2024).[74] Total outpatient attendances. Service code: 370.	£2,290.88 for year 1, £2,512.67 per year for subsequent years

Treatment	Type of monitoring	Unit cost per visit	Frequency of visit	Source	Cost per year
				Medical oncology (consultant led). Frequency: TA721[35] / Clinical expert	
Enzalutamide and apalutamide	Full blood count	£3.10	Every 4 weeks	Type: TA712[75] Unit cost: NHS Cost Collection 2024[74] national average unit cost clinical biochemistry (PATH04) Frequency: TA721[35]	£36
Enzalutamide and apalutamide	Oncology visit	£193.89	Every 4 weeks	Type: TA712[75] Unit cost: National Schedule of NHS Costs (2023/2024).[74] Total outpatient attendances. Service code: 370. Medical oncology (consultant led). Frequency: TA721[35]	£2,512.67

Abbreviations: EAG, External Assessment Group; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; SmPC, summary of product characteristics; TA, technology appraisal

7.1.2.3. Adverse event costs

The annual rate of adverse events (Table 39) for abiraterone were calculated as a weighted average of the rates seen in STAMPEDE and LATITUDE-OLE clinical trial data relative to ADT monotherapy, converted to an annual rate. The annual rates for enzalutamide were converted to annual rates from the ARCHES-OLE clinical trial data relative to ADT monotherapy. For apalutamide, the rates for hypertension, hypokalaemia and ALT increase from TITAN relative to ADT monotherapy were calculated as annual rates. For skin rash the TITAN OLE rate was used and calculated as an annual rate. TITAN-OLE only reported skin rash as an adverse event and TITAN only reported hypertension, hypokalaemia, and ALT increase. The negative cost for enzalutamide is reflective of the reduction in the rate of musculoskeletal events in ARCHES between enzalutamide and ADT.

Musculoskeletal events were reported in ARCHES and STAMPEDE for enzalutamide and abiraterone respectively. In line with expert opinion and NICE TA951[76] (Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer), musculoskeletal

events were defined as spinal cord compression, radiation to bone, surgery to bone, and pathological bone fractures. Data in TA951[76] provided the occurrence of the musculoskeletal events shown in Table 39Table 39 as well as the cost codes to calculate the costs of the events. The EAGs economic analysis adjusted the musculoskeletal event costs by multiplying the unit cost with the occurrence percentage from TA951.[76] While the population in TA951 is different to the population in this analysis (hormone-relapsed vs hormone-sensitive prostate cancer), given its alignment with expert opinion provided to the EAG, these costs and occurrence for musculoskeletal events are considered appropriate for this analysis.

Table 38: Adverse event rates and costs

AE	Abi annual rate	Apa annual rate	Enz annual rate	Cost per event	Cost source
Hypertension	0.0192	-0.0016	0.0077	£90.09	10 minute GP appointment (PSSRU, 2024) 5mg daily dose amlodipine (eMIT[67])
Hypokalaemia	0.0210	0.0004	0.0000	£194.19	Outpatient oncology visit National Schedule of NHS Costs (2023/2024).[74] Total outpatient attendances. Service code: 370. Medical oncology (consultant led) 24mmol daily dose potassium chloride (NICE BNF[77])
ALT increase	0.0103	-0.0004	0.0000	£0.00	N/A
Hyperglycaemia	0.0115	0.0000	0.0000	£0.00	N/A
Musculoskeletal events	0.0086	0.0000	-0.0014	£2,440.47	Sum of events detailed in Table 39Table 39
Erectile disfunction	0.0014	0.0000	0.0000	£0.00	N/A
Hot flushes	0.0007	0.0000	0.0009	£0.00	N/A
Skin rash	0.0005	0.0127	0.0000	£473.00	NHS reference cost 2023/2024 JD07K
Total annual cost per patient (relative to ADT monotherapy)	**£26.28**	**£5.81**	**-£2.61**		

Abbreviations: abi, abiraterone; ALT, alanine aminotransferase; apa, apalutamide; enz, enzalutamide; PSSRU, personal social services research unit.

Table 39: Musculoskeletal events cost

Musculoskeletal event	Occurrence	Cost per event	Adjusted cost per event	Cost source
Spinal cord compression	15.50%	£7,848.26	£1,216.48	NHS reference cost 2023/2024: HC28J non-elective inpatient long stay
Pathological bone fracture	67.70%	£766.97	£519.24	NHS reference cost 2023/2024: Weighted average HD39E, HD39F, HD39G, HD39H. Non-elective inpatient short stay
Radiation to bone	4.10%	£1,015.04	£41.62	NHS reference cost 2023/2023: Weighted average of SC21Z - SC28Z. Outpatient procedures
Surgery to bone	12.90%	£5,140.57	£663.13	NHS reference cost 2023/2024: HD39E non elective patient long stay
Total cost per event		**£14,770.85**	**£2,440.47**	N/A

In sensitivity analysis, an alternative approach to costing adverse events is used, as seen in Clarke 2022.[32] A premium was calculated for cardiac adverse events (myocardial infarction, stroke, transient ischaemic attack, heart failure, angina) and musculoskeletal adverse events (spinal cord compression, long bone fracture, pathological fracture), as the difference between the mean NHS Reference unit cost for treating each type of adverse event, and the mean trial-based cost for an unscheduled visit recorded on the same day as a reported adverse event, applied as a flat rate according to adverse event rate per treatment.

The mean adverse event premium prior to inflation was a flat cost per patient of £137.78 for cardiac adverse events in abiraterone, and £258.03 for musculoskeletal adverse events in abiraterone. Costs following adjustment for inflation are provided in Table 40Table 40.

Table 40: Scenario analysis adverse event costs

Clarke 2022[32] adverse event	Cost per Clarke 2022[32] model time horizon[a]	Annual cost per patient
Cardiac adverse event	£166.38	£3.70
Musculoskeletal adverse event	£311.59	£6.92
Total	**£477.98**	**£10.62**

[a] inflated to 2024 prices from 2017 prices in Clarke 2022.[32]

7.2. Uncertainty analysis

In one way sensitivity analysis and probabilistic sensitivity analysis, adverse event and monitoring unit costs and frequency were varied by 20%. Adverse event rates and monitoring frequency rates were varied probabilistically using a beta distribution, adverse event costs and monitoring costs were varied probabilistically using a normal distribution. Probabilistic sensitivity analysis ran 1,000 iterations of the model.

7.3. Results from the economic modelling

7.3.1. Base case results

Table 41 shows the EAG base case results. The cost of abiraterone over the three year time horizon is lower than enzalutamide by £102,973.39 and apalutamide by £103,011.54. This is driven by the lower treatment cost for abiraterone, at £76.91 per pack vs £2,734.67 and £2,735.00 per pack for enzalutamide and apalutamide respectively (at list price). The monitoring costs for abiraterone are higher than enzalutamide and apalutamide, due to the increased frequency of monitoring required for abiraterone. The cost of adverse events is also higher for abiraterone, driven by the higher rates of adverse events reported in the LATITUDE-OLE and STAMPEDE clinical trial data. The negative adverse event rate cost for enzalutamide is representative of the reduction in key adverse event rates relative to ADT seen in the ARCHES trial.

Table 41: Base case results

Intervention	Treatment costs	Monitoring costs	Adverse event costs	Total cost
Abiraterone	£2,999.49	£8,757.16	£80.89	**£11,837.53**
Enzalutamide	£106,652.13	£8,166.19	£-8.03	**£114,810.29**
Apalutamide	£106,665.00	£8,166.19	£17.89	**£114,849.07**

Table 42 shows the QALY gain required for abiraterone to be no longer considered cost effective compared to enzalutamide and apalutamide at a willingness to pay threshold of £20,000 per QALY. Across the different scenarios tested, comparators would need to generate an additional 3.26 to 4.89 QALYs relative to abiraterone for the cost effectiveness conclusion to change. These values indicate that abiraterone is likely to remain cost effective. The findings from the economic review suggest that a plausible QALY gain for apalutamide relative to abiraterone is between 0.09 and 0.25. The QALY gain for apalutamide in order for abiraterone

to be no longer cost effective from the EAG analysis is 4.89 at a £20k WTP threshold. This is a higher gain than is considered plausible, therefore it is highly likely that abiraterone is cost effective. The findings from the economic review suggest that a plausible QALY gain for enzalutamide relative to abiraterone is between 0and 0.87. The QALY gain for enzalutamide in order for abiraterone to be no longer cost effective from the EAG analysis is 4.88 at a £20k WTP threshold. This is a higher gain than is considered plausible, therefore it is highly likely that abiraterone is cost effective.

Table 42: QALY gain required for abiraterone to be no longer cost effective

Intervention	QALY gain required WTP £20k	QALY gain required WTP £30k
Enzalutamide	4.88	3.26
Apalutamide	4.89	3.26

Abbreviations: QALY, quality adjusted life year; WTP, willingness to pay.

7.3.2. Sensitivity analysis results

7.3.2.1. Deterministic one way sensitivity analysis

To explore the impact of uncertainty in individual model parameters on total costs, a deterministic one-way sensitivity analysis was conducted. Key parameters were varied one at a time across pre-defined ranges. The resulting variation in incremental costs provides insight into which parameters most strongly influence the incremental cost between abiraterone, enzalutamide and apalutamide.

Figure 2 presents the one-way deterministic sensitivity analysis for abiraterone vs enzalutamide. Oncology visit rates for abiraterone and enzalutamide had the largest impact on incremental cost, with differences of £2,792 and £3,025 respectively. Although they were the parameters with the largest impact, the cost saving of abiraterone vs enzalutamide is still between £101,460 and £104,485.

Figure 2: Base case deterministic one way sensitivity analysis abiraterone vs enzalutamide

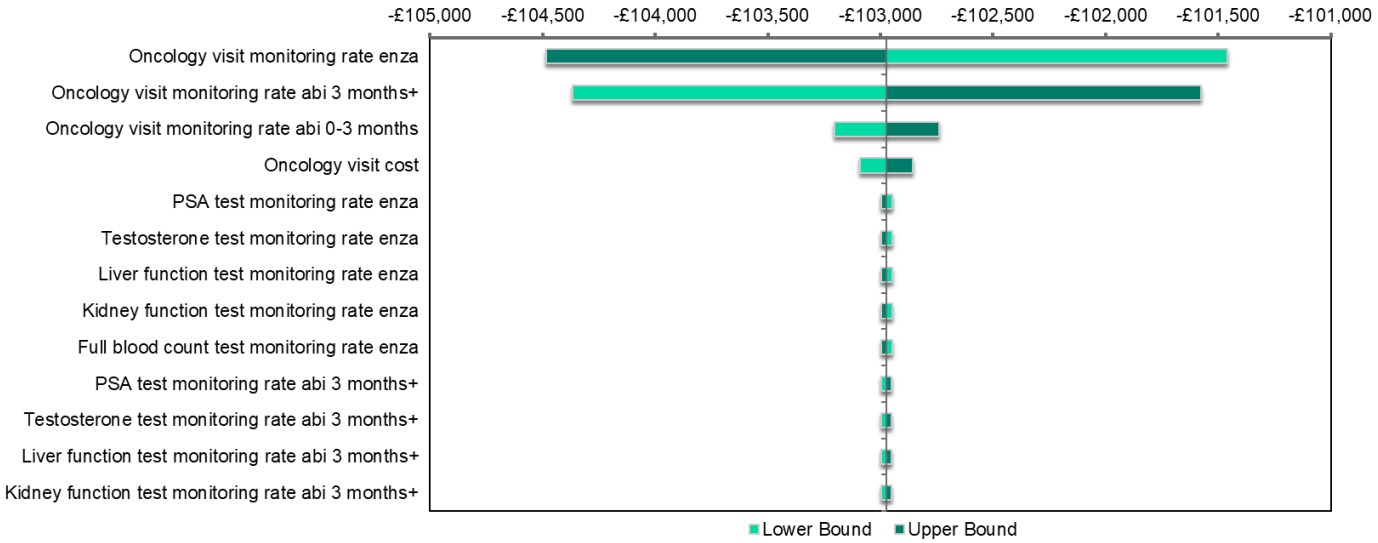
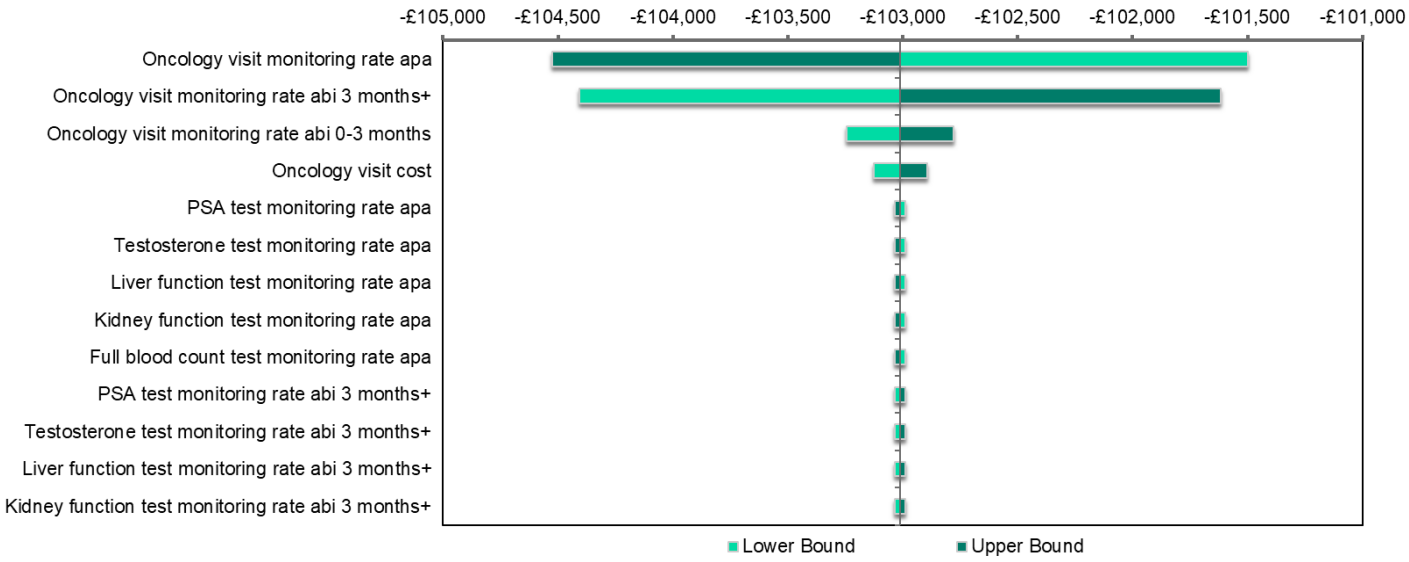


Figure 3 presents the one-way deterministic sensitivity analysis for abiraterone vs apalutamide. Again, oncology visit rates had the largest impact on incremental cost, with differences of £2,792 and £3,025 respectively. The cost saving of abiraterone vs apalutamide was between £101,499 and £104,523.

Figure 3: Deterministic one way sensitivity analysis, incremental cost abiraterone vs apalutamide



7.3.2.2. Probabilistic sensitivity analysis

To assess the overall impact of uncertainty in model parameters for the economic analysis, a probabilistic sensitivity analysis was conducted using 1,000 simulations. Cost and rates of all uncertain parameters were assigned probability distributions reflecting parameter uncertainty. For each of the 1,000 simulations, values were randomly sampled from these distributions and the incremental costs recalculated.

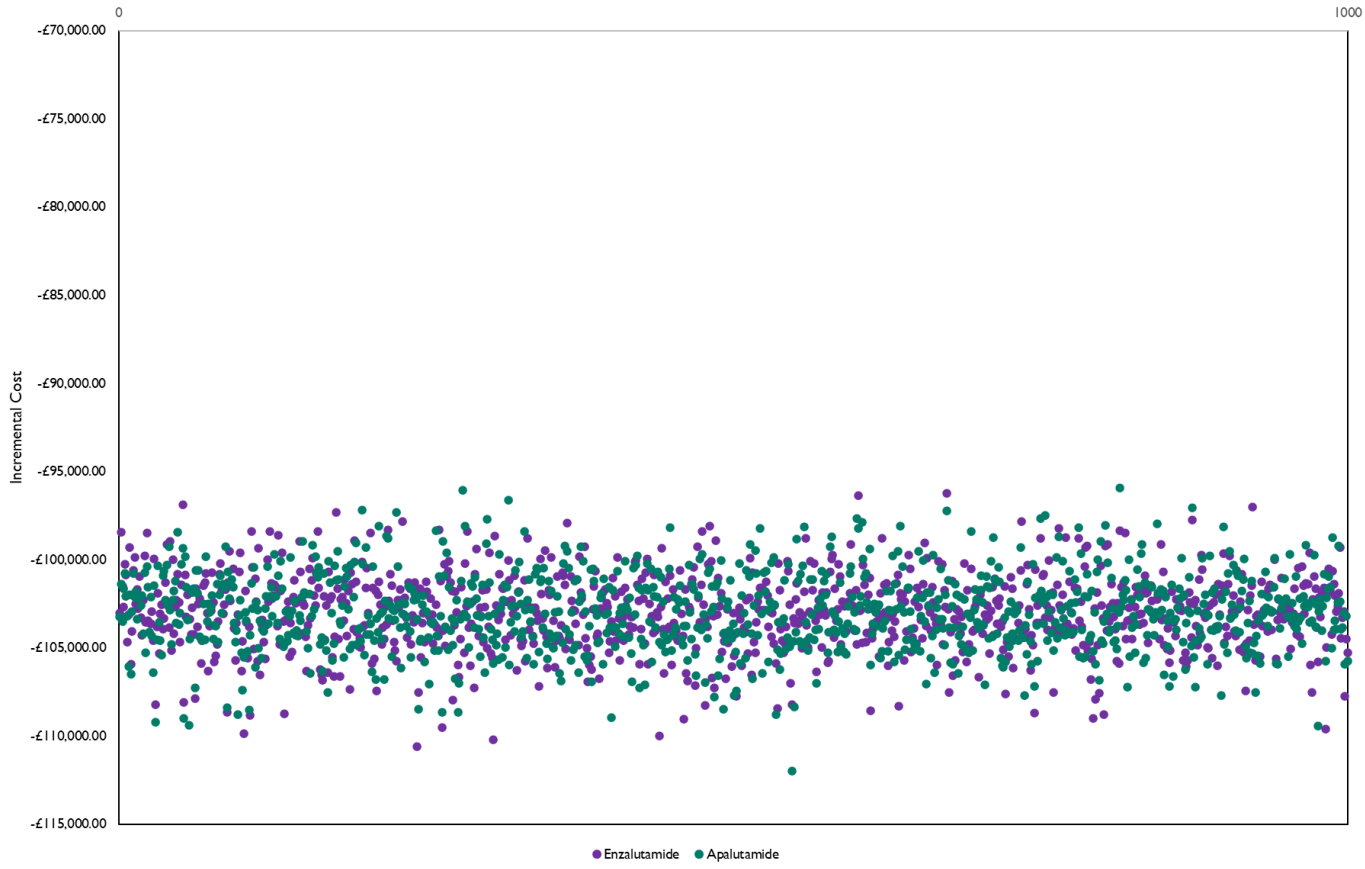
Table 43 presents the mean results of the probabilistic sensitivity analysis over 1,000 simulations. Abiraterone was associated with lower mean costs over a three year time horizon compared with both enzalutamide and apalutamide, with incremental savings ranging from £98,528 and £107,477. 100% of the sample iterations show abiraterone to be cost saving, highlighted in Figure 4. The confidence interval shows the EAG can be 95% confident that the cost saving lies between £98,693 - £107,477 for enzalutamide and £98,528 - £106,937 for apalutamide. This is consistent with the findings from the deterministic sensitivity analysis of cost savings for abiraterone of between £101,460 and £104,523.

Table 43: Probabilistic sensitivity analysis results

Interventions	Total costs	Incremental cost	95% CI lower	95% CI upper
Abiraterone	£11,985	-		
Enzalutamide	£114,945	-£102,960.80	-£107,477.81	-£98,693.12
Apalutamide	£114,857	-£102,872.50	-£106,937.16	-£98,528.52

Abbreviations: CI, confidence interval; PSA, probabilistic sensitivity analysis

Figure 4: Results of PSA



7.3.2.3. Scenario analysis results

Four scenarios were run as part of the economic analysis. Setting the time horizon to two years, setting the relative dose intensity to 95%, reducing the monitoring frequency of apalutamide and enzalutamide, and using the AE patient premium cost estimate from Clarke 2022.[32]

Setting the time horizon to two years has a large impact on the incremental cost difference between abiraterone, enzalutamide and apalutamide due in part to the increased monitoring costs required within year one for abiraterone. This is broadly in line with the median time on treatment in the high-risk population in LATITUDE. The QALY gain required for abiraterone to no longer be cost effective was 3.42 and 3.56 for enzalutamide and apalutamide respectively. Given the QALY gain from apalutamide and enzalutamide estimated from previous economic evaluations of between 0.09-0.25 and 0-0.87 it is expected that in this scenario abiraterone remains highly cost effective.

Scenario analysis exploring the impact of assuming that patients do not fully adhere to the treatment regimen showed a cost saving for abiraterone of £97,970 and £97,828 vs enzalutamide and apalutamide respectively. The QALY gain required in order for abiraterone to be no longer cost effective for this scenario of 4.89 was considerably higher than the range considered plausible. A RDI of 95% was chosen based on data available in TITAN (mean 95.76%).

The reduction in the frequency of treatment monitoring in the enzalutamide and apalutamide arms represents a scenario where a patient does not require as frequent monitoring as abiraterone. The QALY gain required for abiraterone to no longer be cost effective was 5.01 was considerably higher than the range considered plausible.

A scenario using the AE costs from Clarke 2022 were used as an alternative source of AE costs. The QALY gain required for abiraterone to no longer be cost effective was 5.15 was considerably higher than the range considered plausible.

Table 44: Scenario analysis results

	Abiraterone vs enzalutamide		Abiraterone vs apalutamide	
Scenario	**Incremental cost**	**QALY difference required £20k WTP**	**Incremental cost**	**QALY difference required £20k WTP**
Time horizon – 2 years	-£68,452	3.42	-£71,205	3.56
RDI – 95%	-£97,790	4.89	-£97,828	4.89
Less frequent monitoring enzalutamide and apalutamide	-£100,251	5.01	-£100,289	5.01
AE costs Clarke 2022	-£103,062	5.15	-£103,075	5.15

Abbreviations: AE, adverse event; QALY, quality adjusted life year ; RDI, relative dose intensity; WTP, willingness to pay

7.3.3. Summary and interpretation of the economic evidence

The economic analysis compared the costs of abiraterone, enzalutamide and apalutamide from the perspective of the NHS over a three-year time horizon. In the base case, at list price, abiraterone was associated with lower costs than both enzalutamide and apalutamide, driven primarily by differences in acquisition costs. Probabilistic sensitivity analysis indicated that abiraterone remained the least costly option in all simulations. Deterministic sensitivity and scenario analysis showed that the results were most insensitive to the majority of model parameters with the only the time horizon (mean time on treatment) showing any real sensitivity.

When considering treatments at list price the QALY gains required for abiraterone to no longer be cost-effective if abiraterone were less effective than comparators were considerably larger than the range considered plausible based upon previous economic analyses.

Economic analysis including confidential discounts can be found in the cPAS appendix.

References

1. Ellis LM, Bernstein DS, Voest EE, Berlin JD, Sargent D, Cortazar P, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol. 2014;32(12):1277-80.

2. Shore N, Morgans AK, Boegemann M, Gallagher E, Paracha N, Serafini P, et al. Radiological progression-free survival as a surrogate for overall survival in patients with metastatic hormone-sensitive prostate cancer: A bivariate meta-analysis. Eur J Cancer. 2025;223:115513.

3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49.

4. Cancer Research UK. Prostate cancer statistics. London: Cancer Research UK; 2025. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer (accessed 15 July 2025).

5. Tan EH, Burn E, Barclay NL, Delmestri A, Man WY, Golozar A, et al. Incidence, Prevalence, and Survival of Prostate Cancer in the UK. JAMA Netw Open. 2024;7(9):e2434622.

6. Rawla P. Epidemiology of Prostate Cancer. World J Oncol. 2019;10(2):63-89.

7. Lloyd T, Hounsome L, Mehay A, Mee S, Verne J, Cooper A. Lifetime risk of being diagnosed with, or dying from, prostate cancer by major ethnic group in England 2008–2010. BMC Medicine. 2015;13(1):171.

8. National Institute for Health and Care Excellence (NICE). Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases. Technology appraisal guidance TA412. London: NICE; 2016. Available from: https://www.nice.org.uk/guidance/ta412.

9. National Institute for Health and Care Excellence (NICE). Abiraterone (originator and generics) for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer (review of TA721) [ID6378]. Final scope. London: NICE; 2025. Available from: https://www.nice.org.uk/guidance/gid-ta11730/documents/final-scope.

10. National Institute for Health and Care Excellence (NICE). Cost comparison. Addendum to the Guide to the methods of technology appraisal. London: NICE; [2022]. Available from: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf.

11. Centre for Reviews and Dissemination (CRD). Systematic Reviews. CRD's guidance for undertaking reviews in health care. York: University of York; 2009. Available from: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf.

12. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210.

13. Wang T, Wang X, Ding G, Liu H, Ma X, Ma J, et al. Efficacy and safety evaluation of androgen deprivation therapy-based combinations for metastatic castration-sensitive prostate cancer: a systematic review and network meta-analysis. Br J Cancer. 2024;131(8):1363-77.

14. Armstrong AJ, Azad AA, Iguchi T, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, et al. Improved Survival With Enzalutamide in Patients With Metastatic Hormone-Sensitive Prostate Cancer. J Clin Oncol. 2022;40(15):1616-22.

15. Armstrong AJ, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, Villers A, Azad A, et al. ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer. J Clin Oncol. 2019;37(32):2974-86.

16. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev Boris Y, et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med. 2017;377(4):352-60.

17. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. Lancet Oncol. 2019;20(5):686-700.

18. James ND, Bono JSd, Spears MR, Clarke NW, Mason MD, Dearnaley DP, et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N Engl J Med. 2017;377(4):338-51.

19. Hoyle AP, Ali A, James ND, Cook A, Parker CC, de Bono JS, et al. Abiraterone in “High-” and “Low-risk” Metastatic Hormone-sensitive Prostate Cancer. Eur Urol. 2019;76(6):719-28.

20. Attard G, Murphy L, Clarke NW, Sachdeva A, Jones C, Hoyle A, et al. Abiraterone acetate plus prednisolone with or without enzalutamide for patients with metastatic prostate cancer starting androgen deprivation therapy: final results from two randomised phase 3 trials of the STAMPEDE platform protocol. Lancet Oncol. 2023;24(5):443-56.

21. Chi KN, Agarwal N, Bjartell A, Chung BH, Gomes AJPdS, Given R, et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med. 2019;381(1):13-24.

22. Chi KN, Chowdhury S, Bjartell A, Chung BH, Gomes AJPdS, Given R, et al. Apalutamide in Patients With Metastatic Castration-Sensitive Prostate Cancer: Final Survival Analysis of the Randomized, Double-Blind, Phase III TITAN Study. J Clin Oncol. 2021;39(20):2294-303.

23. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.

24. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol. 2008;26(7):1148-59.

25. National Cancer Institute (NCI). NCI Guidelines for Investigators: Adverse event reporting requirements for DCTD (CTEP and CIP) INDs and IDEs. Bethesda (MD): NCI; 2024. Available from: https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events/reporting-requirements.pdf.

26. Schweizer MT, Yu EY. Persistent androgen receptor addiction in castration-resistant prostate cancer. J Hematol Oncol. 2015;8(1):128.

27. Prostate Cancer UK. Treatment options after your first hormone therapy. London: Prostate Cancer UK; 2025.

29. Klaassen Z. ASCO GU 2025: Which Patients with mHSPC Benefit More from Androgen Receptor Pathway Inhibitors? STOPCAP Meta-Analyses of Individual Participant Data. Truckee (CA): UroToday.com; 2025. Available from: https://www.urotoday.com/conference-highlights/asco-gu-2025/asco-gu-2025-prostate-cancer/158138-asco-gu-2025-which-patients-with-mhspc-benefit-more-from-androgen-receptor-pathway-inhibitors-stopcap-meta-analyses-of-individual-participant-data.html.

30. James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N Engl J Med. 2017;377(4):338-51.

31. Kang J, Cairns J, Latimer NR, Duffield S, Grieve R. An assessment of the maturity of cancer survival data used in economic models for the National Institute for Health and Care .

32. Clarke CS, Hunter RM, Gabrio A, Brawley CD, Ingleby FC, Dearnaley DP, et al. Cost-utility analysis of adding abiraterone acetate plus prednisone/prednisolone to long-term hormone therapy in newly diagnosed advanced prostate cancer in England: Lifetime decision model based on STAMPEDE trial data. PLoS One. 2022;17(6):e0269192.

33. Barbier MC, Tomonaga Y, Menges D, Yebyo HG, Haile SR, Puhan MA, et al. Survival modelling and cost-effectiveness analysis of treatments for newly diagnosed metastatic hormone-sensitive prostate cancer. PLoS One. 2022;17(11):e0277282.

34. Naqvi SAA, Faisal KS, Khan MA, Khakwani KZR, Van Houten HK, Moriarty JP, et al. A cost-effectiveness analysis assessing systemic treatments in metastatic castration-sensitive prostate cancer (mCSPC) by volume of disease. J Clin Oncol. 2024;42(4_suppl):93-.

35. National Institute for Health and Care Excellence (NICE). Abiraterone for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer. Technology appraisal guidance TA721. London: NICE; 2021. Available from: https://www.nice.org.uk/guidance/ta721.

36. Gupta N, Gupta D, Vaska KG, Prinja S. Cost-Effectiveness Analysis of Systemic Therapy for Intensification of Treatment in Metastatic Hormone-Sensitive Prostate Cancer in India. Appl Health Econ Health Policy. 2024;22(3):415-26.

37. Handorf EA, Beck JR, Correa A, Ramamurthy C, Geynisman DM. Cost-Effectiveness Analysis for Therapy Sequence in Advanced Cancer: A Microsimulation Approach with Application to Metastatic Prostate Cancer. Med Decis Making. 2023;43(7-8):949-60.

38. Litvin V, Aprikian AG, Dragomir A. Cost-Effectiveness Analysis of Contemporary Advanced Prostate Cancer Treatment Sequences. 32(4).

39. Yoo M, Nelson RE, Haaland B, Dougherty M, Cutshall ZA, Kohli R, et al. Cost-effectiveness analysis of 7 treatments in metastatic hormone-sensitive prostate cancer: a public-payer perspective. J Natl Cancer Inst. 2023;115(11):1374-82.

40. Sathianathen NJ, Lawrentschuk N, Konety B, Azad AA, Corcoran NM, Bolton DM, et al. Cost Effectiveness of Systemic Treatment Intensification for Metastatic Hormone-sensitive Prostate Cancer: Is Triplet Therapy Cost Effective? Eur Urol Oncol. 2024;7(4):870-6.

41. Sung WWY, Choi HCW, Luk PHY, So TH. A Cost-Effectiveness Analysis of Systemic Therapy for Metastatic Hormone-Sensitive Prostate Cancer. Front oncol. 2021;Volume 11 - 2021.

42. Wang L, Hong H, Alexander GC, Brawley OW, Paller CJ, Ballreich J. Cost-Effectiveness of Systemic Treatments for Metastatic Castration-Sensitive Prostate Cancer: An Economic Evaluation Based on Network Meta-Analysis. Value Health. 2022;25(5):796-802.

43. Kyriakopoulos CE, Chen YH, Carducci MA, Liu G, Jarrard DF, Hahn NM, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial. J Clin Oncol. 2018;36(11):1080-7.

44. Clarke NW, Ali A, Ingleby FC, Hoyle A, Amos CL, Attard G, et al. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial. Ann Oncol. 2019;30(12):1992-2003.

45. Armstrong AJ, Iguchi T, Azad AA, Szmulewitz RZ, Holzbeierlein J, Villers A, et al. LBA25 Final overall survival (OS) analysis from ARCHES: A phase III, randomized, double-blind, placebo (PBO)-controlled study of enzalutamide (ENZA) + androgen deprivation therapy (ADT) in men with metastatic hormone-sensitive prostate cancer (mHSPC). Ann Oncol. 2021;32:S1300-S1.

46. Fizazi K, Foulon S, Carles J, Roubaud G, McDermott R, Fléchon A, et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design. Lancet. 2022;399(10336):1695-707.

47. Sweeney CJ, Martin AJ, Stockler MR, Begbie S, Cheung L, Chi KN, et al. Testosterone suppression plus enzalutamide versus testosterone suppression plus standard antiandrogen therapy for metastatic hormone-sensitive prostate cancer (ENZAMET): an international, open-label, randomised, phase 3 trial. Lancet Oncol. 2023;24(4):323-34.

48. Chi KN, Protheroe A, Rodríguez-Antolín A, Facchini G, Suttman H, Matsubara N, et al. Patient-reported outcomes following abiraterone acetate plus prednisone added to androgen deprivation therapy in patients with newly diagnosed metastatic castration-naive prostate cancer (LATITUDE): an international, randomised phase 3 trial. Lancet Oncol. 2018;19(2):194-206.

49. Agarwal N, McQuarrie K, Bjartell A, Chowdhury S, Pereira de Santana Gomes AJ, Chung BH, et al. Health-related quality of life after apalutamide treatment in patients with metastatic castration-sensitive prostate cancer (TITAN): a randomised, placebo-controlled, phase 3 study. Lancet Oncol. 2019;20(11):1518-30.

50. Davis Ian D, Martin Andrew J, Stockler Martin R, Begbie S, Chi Kim N, Chowdhury S, et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. N Engl J Med. 2019;381(2):121-31.

51. Mlcoch T, Decker B, Dolezal T. Cost-Effectiveness Analysis of Parenteral Methotrexate for the Treatment of Crohn's Disease. Appl Health Econ Health Policy. 2021;19(4):593-604.

52. All Wales Therapeutics and Toxicology Centre (AWTTC). Evidence status report for a limited assessment. Abiraterone film-coated tablets. Metastatic hormone sensitive prostate cancer. Reference number: 6441. Penarth: AWTTC; 2025. Available from: https://awttc.nhs.wales/files/assessments-licensed-2025-onwards-esr-recommendation-and-eqhia/evidence-summary-report-abiraterone-6441/.

53. Biologics/Biosimilars. Toronto: pCPA; 2025. Available from: https://www.pcpacanada.ca/biologics-biosimilars.

54. Hughes A, Marshall JK, Moretti ME, Ungar WJ. A cost-utility analysis of biosimilar infliximab compared to reference infliximab in adult switch patients with Crohn's disease: a Canadian analysis. Full Report. Report No. 2019-02. Toronto: The Hospital for Sick Children; 2019. Available from: https://lab.research.sickkids.ca/task/wp-content/uploads/sites/66/2019/02/CUA_Biosimilar_Infliximab_CD_FULLREPORT_2019-02.pdf.

55. Scottish Medicines Consortium (SMC). Biosimilar medicines. Glasgow: SMC; 2015. Available from: https://scottishmedicines.org.uk/media/2836/biosimilar-medicines.pdf.

56. Institute for Clinical and Economic Review (ICER). ICER's Reference Case for Economic Evaluations: Elements and Rationale. Boston: ICER; 2024. Available from: https://icer.org/wp-content/uploads/2024/02/Reference-Case-4.3.25.pdf.

57. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual. PMG36. London: NICE; 2022. Available from: https://www.nice.org.uk/process/pmg36/ (accessed 14 Jul 2025).

58. Jørgensen KK, Olsen IC, Goll GL, Lorentzen M, Bolstad N, Haavardsholm EA, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet. 2017;389(10086):2304-16.

59. Lehmann M, Arbo E, Pouly J-L, Barrière P, Boland LA, Bean SG, et al. Determining the cost-effectiveness of follitropin alfa biosimilar compared to follitropin alfa originator in women undergoing fertility treatment in France. Eur J Obstet Gynecol Reprod Biol X. 2024;22:100311.

60. Sarzi-Puttini P, Marotto D, Caporali R, Galeazzi M, Atzeni F, Hamar A, et al. Biosimilars vs originators: Are they the same? Autoimmun Rev. 2019;18(12):102404.

61. Chen MKY, Vissapragada R, Bulamu N, Gupta M, Werth V, Sebaratnam DF. Cost-Utility Analysis of Rituximab vs Mycophenolate Mofetil for the Treatment of Pemphigus Vulgaris. JAMA Dermatol. 2022;158(9):1013-21.

62. Peng K, Chan SCW, Wang Y, Cheng FWT, Yeung WWY, Jiao Y, et al. EE729 Early Intervention With Biosimilars Compared With Leflunomide in Established Rheumatoid Arthritis: A Cost-Effectiveness Analysis in Hong Kong. Value Health. 2023;26(12):S195.

63. Hegde NC, Kumar A, Kaundal S, Saha L, Malhotra P, Prinja S, et al. Generic ibrutinib a potential cost-effective strategy for the first-line treatment of chronic lymphocytic leukaemia. Ann Hematol. 2023;102(11):3125-32.

64. Cornes P, Kelton J, Liu R, Zaidi O, Stephens J, Yang J. Real-world cost-effectiveness of primary prophylaxis with G-CSF biosimilars in patients at intermediate/high risk of febrile neutropenia. Future Oncol. 2022.

65. All Wales Therapeutics and Toxicology Centre (AWTTC). filgrastim (Ratiograstim®). Penarth: AWTTC; 2009. Available from: https://awttc.nhs.wales/accessing-medicines/medicine-recommendations/filgrastim-ratiograstim/.

66. Clarke K, Ainslie-Garcia M, Ferko N, Shastri K. Modelling the opportunity for cost-savings or patient access with biosimilar adalimumab and tocilizumab: a European perspective. J Med Econ. 2024;27(1):952-62.

67. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT). London: UK Department of Health and Social Care 2011 [updated 23 Oct 2024]. Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit.

68. British National Formulary (BNF). Enzalutamide. Medicinal forms. London: BMJ Publishing Group Ltd and the Royal Pharmaceutical Society of Great Britain; 2025. Available from: https://bnf.nice.org.uk/drugs/enzalutamide/medicinal-forms/ (accessed 15 Jul 2025).

69. British National Formulary (BNF). Apalutamide. Medicinal forms. London: BMJ Publishing Group Ltd and the Royal Pharmaceutical Society of Great Britain; 2025. Available from: https://bnf.nice.org.uk/drugs/apalutamide/medicinal-forms/ (accessed 15 Jul 2025).

70. electronic medicines compendium (emc). Abiraterone 500 mg film-coated tablets. SmPC. Leatherhead: Datapharm Ltd; 2023 [updated 22 Nov 2023]. Available from: https://www.medicines.org.uk/emc/product/14010/smpc.

71. electronic medicines compendium (emc). Prednisolone 5mg Tablets. Leatherhead: Datapharm Ltd; 2021 [updated 25 May 2021].

74. NHS England (NHSE). National Cost Collection for the NHS. London: NHSE; 2024. Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/.

75. National Institute for Health and Care Excellence (NICE). Enzalutamide for treating hormone-sensitive metastatic prostate cancer. Technology appraisal guidance TA712. London: NICE; 2021. Available from: https://www.nice.org.uk/guidance/ta712.

76. National Institute for Health and Care Excellence (NICE). Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer. Technology appraisal guidance TA951. London: NICE; 2024. Available from: https://www.nice.org.uk/guidance/ta951.

77. British National Formulary (BNF). Potassium chloride with potassium bicarbonate. Medicinal forms. London: BMJ Publishing Group Ltd and the Royal Pharmaceutical Society of Great Britain; 2025. Available from: https://bnf.nice.org.uk/drugs/potassium-chloride-with-potassium-bicarbonate/medicinal-forms/ (accessed 01 Aug 2025).

78. Azad AA, Armstrong AJ, Alcaraz A, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, et al. Efficacy of enzalutamide in subgroups of men with metastatic hormone-sensitive prostate cancer based on prior therapy, disease volume, and risk - supplementary material. Prostate Cancer Prostatic Dis. 2022;25(2).

79. Jian T, Zhan Y, Yu Y, Yu K, Hu R, Wang J, et al. Combination therapy for high-volume versus low-volume metastatic hormone-sensitive prostate cancer: A systematic review and network meta-analysis. Front Pharmacol. 2023;Volume 14 - 2023.

80. Zhou Z, Liu S, Mei J, Liu T, Liu F, Zhang G. Systemic therapies for high-volume metastatic hormone-sensitive prostate cancer: a network meta-analysis. Acta Oncologica. 2023;62(9):1083-90.

Appendix A: Search strategies

Search strategies

Clinical (SRs/MAs)

Database(s): **Ovid MEDLINE(R) ALL** 1946 to May 29, 2025
Search Strategy:

#	Searches	Results
1	Prostatic Neoplasms/	152556
2	prostat*.ti,ab.	273936
3	(cancer or carcinoma or malignant or malignancy or tumor or tumoral or tumour or adenocarcinoma).ti,ab.	3979756
4	2 and 3	204227
5	4 or 1	226437
6	(metastatic or mHSPC or metastasized or metastasised or advanced or disseminated).ti,ab.	986704
7	5 and 6	42769
8	(Enzalutamide or Xtandi).ti,ab,kw.	3501
9	(Abiraterone or Zytiga).ti,ab,kw.	3459
10	Abiraterone Acetate/	783
11	(Apalutamide or Erleada).ti,ab,kw.	634
12	or/8-11	5557
13	(systematic review or meta-analysis).pt.	380583
14	meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/	426336
15	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.	419274
16	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.	19973
17	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.	46924
18	(data synthes* or data extraction* or data abstraction*).ti,ab,kf.	51950
19	(handsearch* or hand search*).ti,ab,kf.	12084
20	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.	41566
21	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.	14188
22	(meta regression* or metaregression*).ti,ab,kf.	18649
23	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	578242
24	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.	432934
25	(cochrane or (health adj2 technology assessment) or evidence report).jw.	22564
26	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf.	21369
27	(outcomes research or relative effectiveness).ti,ab,kf.	12374
28	((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.	5036
29	(meta-analysis or systematic review).mp.	540690
30	(multi* adj3 treatment adj3 comparison*).ti,ab,kf.	336
31	(mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.	185
32	umbrella review*.ti,ab,kf.	2792
33	(multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	15
34	(multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.	19

35	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	13
36	or/13-35	840996
37	7 and 12 and 36	347
38	limit 37 to yr="2020 -Current"	209

Database(s): **Embase** 1974 to 2025 June 04
Search Strategy:

#	Searches	Results
1	prostate cancer/ or metastatic prostate cancer/ or metastatic castration sensitive prostate cancer/	253483
2	prostat*.ti,ab.	406748
3	(cancer or carcinoma or malignant or malignancy or tumor or tumoral or tumour or adenocarcinoma).ti,ab.	5497054
4	2 and 3	313667
5	4 or 1	366902
6	(metastatic or mHSPC or metastasized or metastasised or advanced or disseminated).ti,ab.	1495531
7	5 and 6	77734
8	(Enzalutamide or Xtandi).ti,ab,kw.	7894
9	enzalutamide/	12373
10	(Abiraterone or Zytiga).ti,ab,kw.	8057
11	abiraterone acetate/ or abiraterone/	11954
12	(Apalutamide or Erleada).ti,ab,kw.	1418
13	apalutamide/	2483
14	or/8-13	18604
15	(systematic review or meta-analysis).pt.	0
16	meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/	760847
17	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.	502215
18	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.	22769
19	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.	65449
20	(data synthes* or data extraction* or data abstraction*).ti,ab,kf.	62471
21	(handsearch* or hand search*).ti,ab,kf.	14643
22	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.	55045
23	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.	24353
24	(meta regression* or metaregression*).ti,ab,kf.	22510
25	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	897090
26	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.	554560
27	(cochrane or (health adj2 technology assessment) or evidence report).jw.	32812
28	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf.	32317
29	(outcomes research or relative effectiveness).ti,ab,kf.	18282
30	((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.	8802
31	(meta-analysis or systematic review).mp.	848734
32	(multi* adj3 treatment adj3 comparison*).ti,ab,kf.	479
33	(mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.	266
34	umbrella review*.ti,ab,kf.	2928
35	(multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	37

36	(multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.	22
37	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	31
38	or/15-37	1197035
39	7 and 14 and 38	853
40	limit 39 to yr="2020 -Current"	500

Cochrane CDSR

Search Name: abiraterone
Date Run: 03/06/2025 09:45:53
Comment:

ID Search Hits
#1 MeSH descriptor: [Prostatic Neoplasms] explode all trees 9071
#2 (prostat*):ti,ab,kw 28834
#3 ((cancer or carcinoma or malignant or malignancy or tumor or tumoral or tumour or adenocarcinoma)):ti,ab,kw 273499
#4 #2 and #3 19395
#5 #4 or #1 19922
#6 ((metastatic or mHSPC or metastasized or metastasised or advanced or disseminated)):ti,ab,kw 104282
#7 #5 and #6 6555
#8 (Enzalutamide or Xtandi):ti,ab,kw 1224
#9 (Abiraterone or Zytiga):ti,ab,kw 1381
#10 MeSH descriptor: [Abiraterone Acetate] explode all trees 246
#11 (Apalutamide or Erleada):ti,ab,kw 379
#12 #8 or #9 or #10 #11 1989
#13 #7 and #12 1576

Of which, Cochrane Reviews = 2

INAHTA

(Enzalutamide or Xtandi or Abiraterone or Zytiga or Apalutamide or Erleada) limited to 2020-2025
N = 21

Clinical (RCTs)

Database(s): **Ovid MEDLINE(R) ALL** 1946 to June 26, 2025
Search Strategy:

#	Searches	Results
1	Prostatic Neoplasms/	152927
2	prostat*.ti,ab.	274980
3	(cancer or carcinoma or malignant or malignancy or tumor or tumoral or tumour or adenocarcinoma).ti,ab.	3996712
4	2 and 3	205090
5	4 or 1	227317
6	(metastatic or mHSPC or metastasized or metastasised or advanced or disseminated).ti,ab.	993383
7	5 and 6	43006
8	(Enzalutamide or Xtandi).ti,ab,kw.	3528
9	(Abiraterone or Zytiga).ti,ab,kw.	3485

10	Abiraterone Acetate/	784
11	(Apalutamide or Erleada).ti,ab,kw.	641
12	or/8-11	5598
13	exp randomized controlled trial/	643136
14	controlled clinical trial.pt.	95710
15	randomized.ab.	698200
16	placebo.ab.	259889
17	drug therapy.fs.	2826634
18	randomly.ab.	463038
19	trial.ab.	761220
20	groups.ab.	2873873
21	or/13-20	6330685
22	7 and 12 and 21	2552
23	limit 22 to yr="2024 -Current"	381

Database(s): **Embase** 1974 to 2025 June 26
Search Strategy:

#	Searches	Results
1	prostate cancer/ or metastatic prostate cancer/ or metastatic castration sensitive prostate cancer/	255977
2	prostat*.ti,ab.	409750
3	(cancer or carcinoma or malignant or malignancy or tumor or tumoral or tumour or adenocarcinoma).ti,ab.	5537576
4	2 and 3	316242
5	4 or 1	369761
6	(metastatic or mHSPC or metastasized or metastasised or advanced or disseminated).ti,ab.	1515552
7	5 and 6	78820
8	(Enzalutamide or Xtandi).ti,ab,kw.	8037
9	enzalutamide/	12546
10	(Abiraterone or Zytiga).ti,ab,kw.	8202
11	abiraterone acetate/ or abiraterone/	12126
12	(Apalutamide or Erleada).ti,ab,kw.	1481
13	apalutamide/	2561
14	or/8-13	18886
15	exp randomized controlled trial/	1086329
16	Controlled clinical trial/	459653
17	random$.ti,ab.	2450524
18	randomization/	100931
19	intermethod comparison/	314819
20	placebo.ti,ab.	458957
21	(compare or compared or comparison).ti.	682866
22	((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.	3268067
23	(open adj label).ti,ab.	184132
24	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.	363639
25	double blind procedure/	304910
26	parallel group$1.ti,ab.	52224
27	(crossover or cross over).ti,ab.	154693
28	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.	502734
29	(assigned or allocated).ti,ab.	597639

30	(controlled adj7 (study or design or trial)).ti,ab.	623718
31	(volunteer or volunteers).ti,ab.	320211
32	human experiment/	719275
33	trial.ti.	549789
34	or/15-33	7385929
35	(random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)	10542
36	Cross-sectional study/ not (exp randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)	452478
37	(((case adj control$) and random$) not randomi?ed controlled).ti,ab.	24201
38	Systematic review.ti,ab. not (trial or study).ti.	408779
39	(nonrandom$ not random$).ti,ab.	21117
40	"random field$".ti,ab.	3182
41	(random cluster adj3 sampl$).ti,ab.	1769
42	(review.ab. and review.pt.) not trial.ti.	1298028
43	"we searched".ab. and (review.ti. or review.pt.)	58552
44	"update review".ab.	154
45	(databases adj4 searched).ab.	77026
46	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/	1305500
47	Animal experiment/ not (human experiment/ or human/)	2754380
48	or/35-47	4905460
49	34 not 48	6505163
50	7 and 14 and 49	4009
51	limit 50 to yr="2024 -Current"	527

Cochrane Trials

Search Name: abiraterone
Date Run: 27/06/2025 15:21:52
Comment:

ID Search Hits
#1 MeSH descriptor: [Prostatic Neoplasms] explode all trees 9071
#2 (prostat*):ti,ab,kw 28834
#3 ((cancer or carcinoma or malignant or malignancy or tumor or tumoral or tumour or adenocarcinoma)):ti,ab,kw 273499
#4 #2 and #3 19395
#5 #4 or #1 19922
#6 ((metastatic or mHSPC or metastasized or metastasised or advanced or disseminated)):ti,ab,kw 104282
#7 #5 and #6 6555
#8 (Enzalutamide or Xtandi):ti,ab,kw 1224
#9 (Abiraterone or Zytiga):ti,ab,kw 1381
#10 MeSH descriptor: [Abiraterone Acetate] explode all trees 246
#11 (Apalutamide or Erleada):ti,ab,kw 379
#12 #8 or #9 or #10 #11 1989
#13 #7 and #12 with Cochrane Library publication date from Jan 2024 to present 287

Of which, Cochrane Trials = 287

Economic studies

Database(s): **Ovid MEDLINE(R) ALL** 1946 to June 04, 2025
Search Strategy:

#	Searches	Results
1	Prostatic Neoplasms/	152726
2	prostat*.ti,ab.	274226
3	(cancer or carcinoma or malignant or malignancy or tumor or tumoral or tumour or adenocarcinoma).ti,ab.	3984483
4	2 and 3	204480
5	4 or 1	226695
6	(metastatic or mHSPC or metastasized or metastasised or advanced or disseminated).ti,ab.	988436
7	5 and 6	42856
8	(Abiraterone or Zytiga).ti,ab,kw.	3468
9	7 and 8	2482
10	Economics/	27545
11	exp "Costs and Cost Analysis"/	279411
12	Economics, Nursing/	4013
13	Economics, Medical/	9304
14	Economics, Pharmaceutical/	3163
15	exp Economics, Hospital/	26216
16	Economics, Dental/	1922
17	exp "Fees and Charges"/	31693
18	exp Budgets/	14360
19	budget*.ti,ab,kf.	40409
20	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	314122
21	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	441624
22	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	249739
23	(value adj2 (money or monetary)).ti,ab,kf.	3445
24	exp models, economic/	16846
25	economic model*.ab,kf.	4766
26	markov chains/	17126
27	markov.ti,ab,kf.	33078
28	monte carlo method/	34251
29	monte carlo.ti,ab,kf.	67045
30	exp Decision Theory/	14345
31	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	50393
32	or/10-31	1016459
33	9 and 32	132
34	**limit 33 to yr="2021 -Current" [previous economic evaluations]**	**54**
35	*Biosimilar Pharmaceuticals/	3549
36	*Drugs, Generic/	4240
37	or/24-31	176025
38	(35 or 36) and 37	136
39	**limit 38 to yr="2021 -Current" [biosimilars and generics]**	**40**

Database(s): **Embase** 1974 to 2025 July 08
Search Strategy:

#	Searches	Results
1	prostate cancer/ or metastatic prostate cancer/ or metastatic castration sensitive prostate cancer/	256721
2	prostat*.ti,ab.	410728
3	(cancer or carcinoma or malignant or malignancy or tumor or tumoral or tumour or adenocarcinoma).ti,ab.	5555775
4	2 and 3	317126
5	4 or 1	370747
6	(metastatic or mHSPC or metastasized or metastasised or advanced or disseminated).ti,ab.	1521744
7	5 and 6	79175
8	(Abiraterone or Zytiga).ti,ab,kw.	8235
9	abiraterone acetate/ or abiraterone/	12174
10	8 or 9	12896
11	Economics/	246697
12	Cost/	66167
13	exp Health Economics/	1156748
14	Budget/	36910
15	budget*.ti,ab,kf.	54111
16	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	388056
17	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	634288
18	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	351187
19	(value adj2 (money or monetary)).ti,ab,kf.	4642
20	Statistical Model/	181508
21	economic model*.ab,kf.	7246
22	Probability/	171680
23	markov.ti,ab,kf.	43462
24	monte carlo method/	58169
25	monte carlo.ti,ab,kf.	71435
26	Decision Theory/	1923
27	Decision Tree/	29298
28	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	67060
29	or/11-28	2283783
30	10 and 29	1572
31	limit 30 to yr="2021 -Current"	627
32	limit 31 to "remove clinical trial (clinicaltrials.gov) records"	620
33	(conference or conference abstract or conference paper or "conference review").pt.	6323726
34	limit 33 to yr="2020 - 2023"	1291132
35	**32 not 34 [previous economic evaluations]**	**439**
36	*biosimilar agent/	5269
37	*generic drug/	6034
38	36 or 37	11194
39	or/20-28	512403
40	38 and 39	186
41	**limit 40 to yr="2021 -Current" [biosimilars and generics]**	**78**

INAHTA [previous economic evaluations]

(Enzalutamide or Xtandi or Abiraterone or Zytiga or Apalutamide or Erleada) limited to 2020-2025

N = 21

INAHTA [biosimilars and generics]
"Biosimilar Pharmaceuticals"[mh] OR "Drugs, Generic"[mh] OR generic* or biosimilar*
N = 145

CEA ("Methods", 2021 - present) [previous economic evaluations]
Abiraterone
N = 9

CEA ("Methods", 2021 - present) [biosimilars and generics]
biosimilar*
N = 32

generic*
N = 32

Methods documents searches [biosimilars and generics]

- National Institute for Health and Care Excellence (NICE): England and Wales
- Scottish Medicines Consortium (SMC): Scotland
- All Wales Medicines Strategy Group (AWMSG): Wales
- Canada's Drug Agency (CDA-AMC): Canada
- Haute Autorité de Santé (HAS): France
- Institute for Clinical and Economic Review (ICER): USA
- European Network for Health Technology Assessment (EUnetHTA): Europe
- Dental and Pharmaceutical Benefits Agency (TLV): Sweden
- National Health Care Institute (ZIN): The Netherlands
- Pharmaceutical Benefits Advisory Committee (PBAC): Australia

N = 8

Appendix B: PRISMA flow diagrams

Figure 5: PRISMA of SLR/MA search

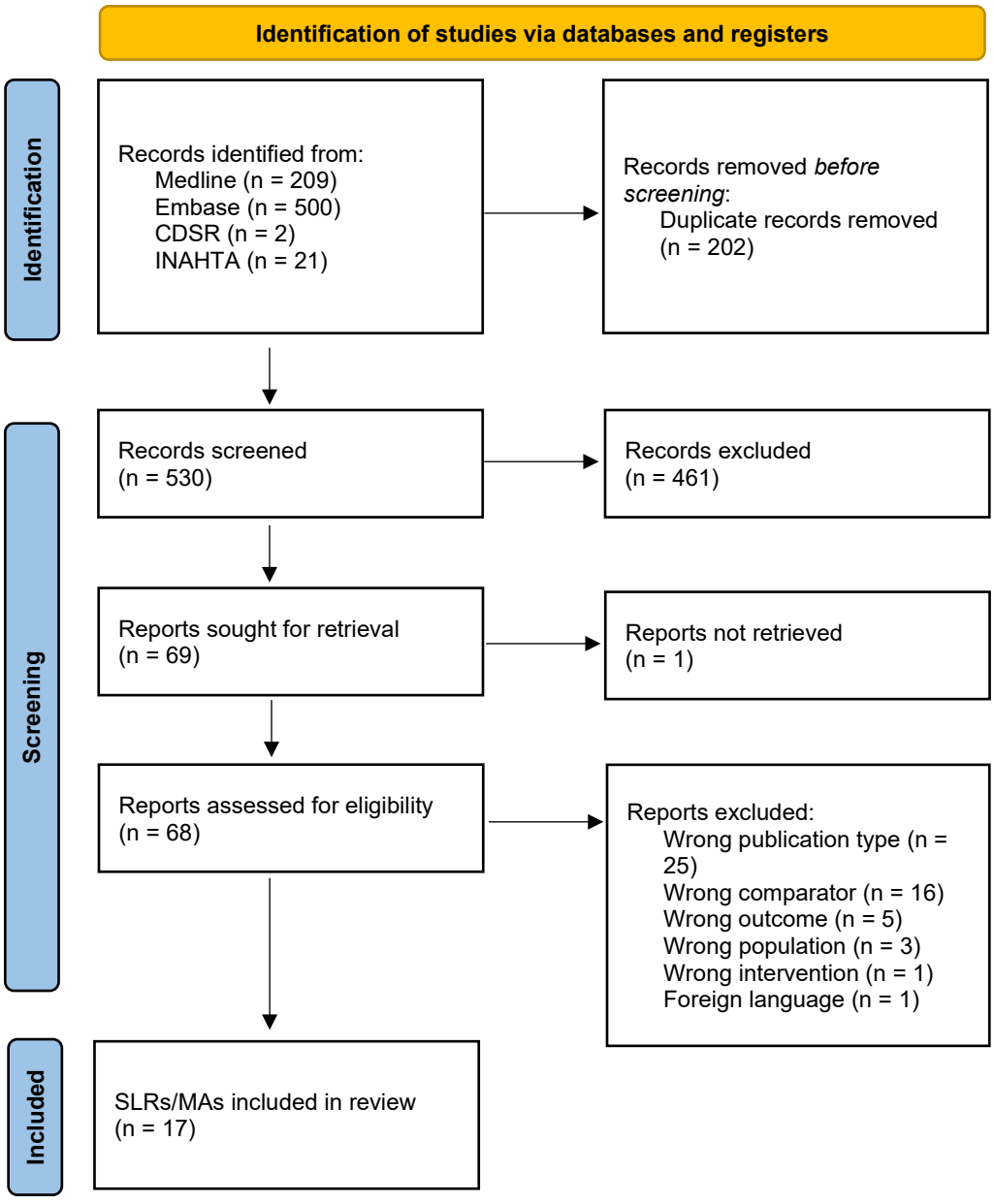


Figure 6: PRISMA of RCT update search

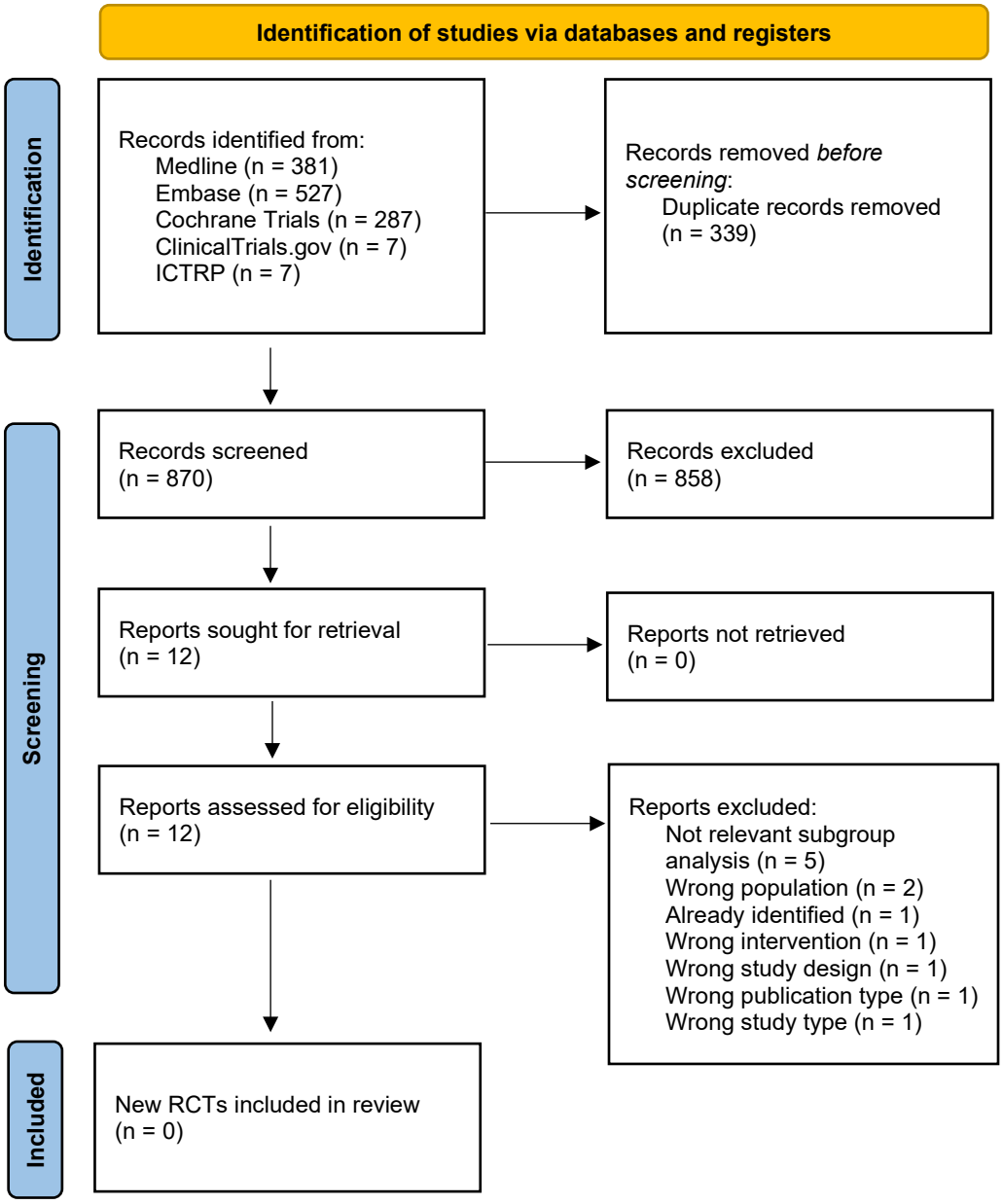


Figure 7: PRISMA of previous economic evaluations search

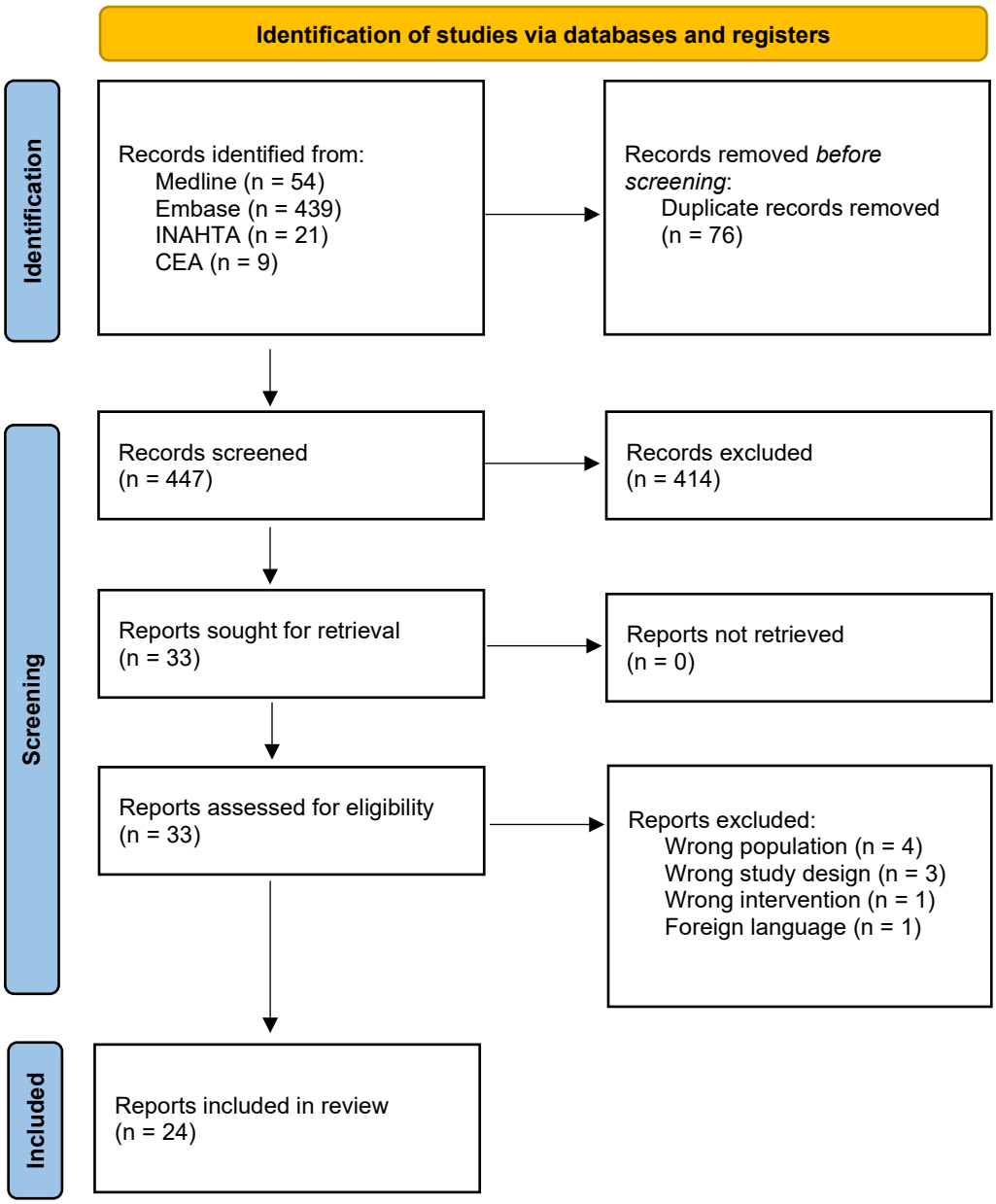
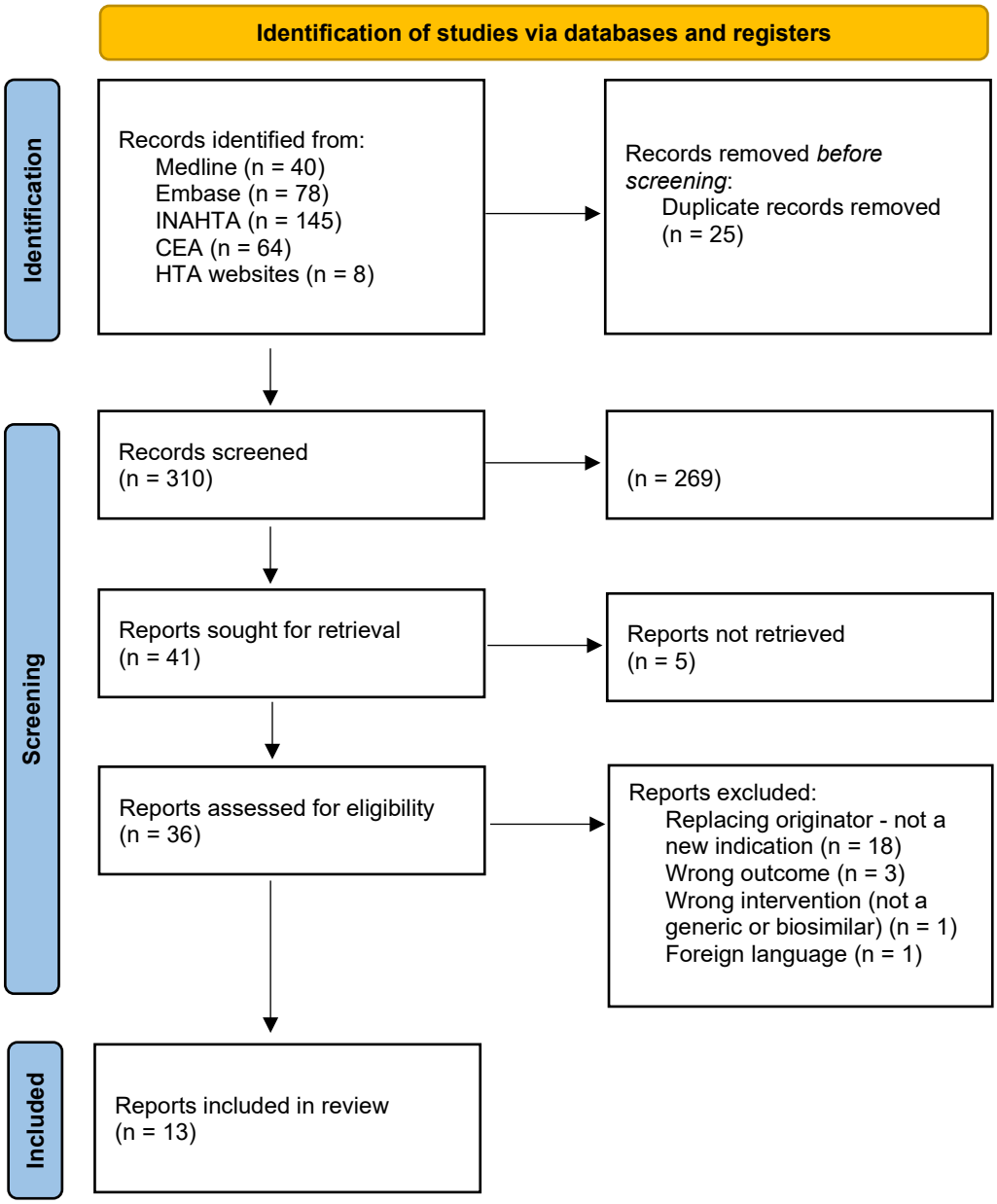


Figure 8: PRISMA of search for literature related to the assessment of biosimilars and generics



Appendix C: Full text excludes

Table 45: Full text excludes - SLR/MA search

First author	Year	Title	Reasons for exclusion
Avxentyev et al.	2024	Clinical and economic impact of modern pharmaceuticals on reducing mortality from hormone-sensitive prostate cancer with high-volume disease	Foreign language
Aziz et al.	2023	A Systematic Review and Network Meta-Analysis of Metastatic Hormone-Sensitive Prostate Cancer Therapy Cardiotoxicity	Wrong publication type (abstract)
Cao et al.	2022	Adverse events associated with androgen receptor signaling inhibitors in the treatment of prostate cancer: A systematic review and network meta-analysis	Wrong publication type (abstract)
Cao et al.	2023	Adverse Events and Androgen Receptor Signaling Inhibitors in the Treatment of Prostate Cancer: A Systematic Review and Multivariate Network Meta-analysis	Wrong comparator
Chen et al.	2020	Comparison of current systemic combination therapies for metastatic hormone-sensitive prostate cancer and selection of candidates for optimal treatment: A systematic review and Bayesian network meta-analysis	Wrong publication type (abstract)
Chen et al.	2023	Comparative efficacy of second-generation androgen receptor inhibitors for treating prostate cancer: A systematic review and network meta-analysis	Wrong comparator
Di Maio et al.	2023	A network meta-analysis on the safety of systemic treatments in metastatic hormonesensitive prostate cancer patients	Wrong publication type (abstract)
Dou et al.	2023	Based on ARASENS trial: efficacy and safety of darolutamide as an emerging option of endocrinotherapy for metastatic hormone-sensitive prostate cancer-an updated systematic review and network meta-analysis	Wrong comparator
Fan et al.	2020	Oncology control of novel treatment regimens of metastatic low-volume hormone-sensitive prostate cancer: A Bayesian network meta-analysis	Wrong publication type (abstract)
Fisher et al.	2025	Which patients with metastatic hormone-sensitive prostate cancer (mHSPC) benefit more from androgen receptor pathway inhibitors (ARPIs)? STOPCAP metaanalyses of individual participant data (IPD)	Wrong publication type (abstract)
Haddad et al.	2020	Comparative efficacy of first-line novel anti-androgen therapies versus docetaxel in metastatic hormone sensitive prostate cancer (mHSPC): An updated network meta-analysis	Wrong publication type (abstract)
Hoeh et al.	2024	Triplet or Doublet Therapy in Metastatic Hormone-sensitive Prostate Cancer Patients: An Updated Network Meta-analysis Including ARANOTE Data	Wrong comparator

First author	Year	Title	Reasons for exclusion
Huang et al.	2023	Risk of cognitive impairment in men with advanced prostate cancer treated with NHAs: A systematic review and network meta-analysis	Wrong comparator,wrong population
Jian et al.	2022	Systemic triplet therapy for metastatic hormone-sensitive prostate cancer: A systematic review and network meta-analysis	Wrong comparator
Kohli et al.	2023	Cost-effectiveness analysis of seven treatment regimens in metastatic hormone-sensitive prostate cancer (mHSPC): A public payer perspective using network meta-analysis	Wrong publication type (abstract)
Kumar et al.	2022	Combination therapy in metastatic castration sensitive prostate cancer: A Systematic review and network meta-analysis	Wrong outcome
Lee et al.	2023	Oral chemotherapeutic agents in metastatic hormone-sensitive prostate cancer: A network meta-analysis of randomized controlled trials	Wrong comparator
Li et al.	2024	Sequential versus concomitant treatment of androgen receptor signaling inhibitors and docetaxel for metastatic hormone-sensitive prostate cancer: an network meta-analysis	Wrong comparator
Mandel et al.	2023	Triplet or Doublet Therapy in Metastatic Hormone-sensitive Prostate Cancer Patients: A Systematic Review and Network Meta-analysis	Wrong outcome
Mansourian et al.	2020	Comparative Effectiveness of All Available Treatments for Metastatic Hormone-Sensitive Prostate Cancer: A Network Meta-analysis	Wrong population
Matsukawa et al.	2025	An Updated Systematic Review and Network Meta-Analysis of First-Line Triplet vs. Doublet Therapies for Metastatic Hormone-Sensitive Prostate Cancer	Wrong comparator
Matsukawa et al.	2024	Impact of disease volume on survival efficacy of triplet therapy for metastatic hormone-sensitive prostate cancer: a systematic review, meta-analysis, and network meta-analysis	Wrong comparator
Matsukawa et al.	2024	Evaluation of cardiovascular events among men with prostate cancer treated with androgen receptor signaling inhibitors: a systematic review, meta-analysis and network meta-analysis	Wrong publication type (abstract)
Matsukawa et al.	2025	Cardiovascular events among men with prostate cancer treated with androgen receptor signaling inhibitors: a systematic review, meta-analysis, and network meta-analysis	Wrong comparator
Matsukawa et al.	2024	Evaluation of cardiovascular events among men with prostate cancer treated with androgen receptor signaling inhibitors: A systematic review, meta-analysis, and network meta-analysis	Wrong publication type (abstract)
Matsukawa et al.	2025	Central Nervous System Toxicity in Prostate Cancer Patients Treated with Androgen Receptor Signaling Inhibitors: A Systematic Review, Meta-analysis, and Network Meta-analysis	Wrong comparator
Morales et al.	2024	Comparative health-related quality of life (QoL) in metastatic castration-sensitive prostate cancer (mCSPC): A living systematic review	Wrong publication type (abstract)
Naqvi et al.	2025	Choice of androgen receptor pathway inhibitors (ARPI) by disease volume and timing of metastases in metastatic hormone sensitive	Wrong publication type (abstract)

First author	Year	Title	Reasons for exclusion
		prostate cancer (mHSPC)	
Naqvi et al.	2024	Comparative survival in metastatic castration-sensitive prostate cancer (mCSPC) by prognostic subgroups: A living network meta-analysis	Wrong publication type (abstract)
Ohlmann et al.	2022	An adjusted indirect treatment comparison (ITC) of enzalutamide (ENZ) versus docetaxel (DOC) for metastatic hormone-sensitive prostate cancer (mHSPC)	Wrong publication type (abstract)
Riaz et al.	2022	First-line treatment options in metastatic castration-sensitive prostate cancer: A systematic review and network meta-analysis	Wrong publication type (abstract)
Riaz et al.	2022	1417P Mixed treatment comparisons evaluating contemporary therapies in metastatic castration sensitive prostate cancer (mCSPC): A living systematic review	Wrong publication type (abstract)
Riaz et al.	2023	A living interactive systematic review and network meta-analysis evaluating systemic therapies in metastatic castration-sensitive prostate cancer (mCSPC)	Wrong publication type (abstract)
Roy et al.	2022	Addition of Docetaxel to Androgen Receptor Axis-targeted Therapy and Androgen Deprivation Therapy in Metastatic Hormone-sensitive Prostate Cancer: A Network Meta-analysis	Wrong comparator
Saad et al.	2022	Cost-effectiveness of enzalutamide versus apalutamide versus androgen deprivation therapy alone for the treatment of metastatic castration-sensitive prostate cancer in Canada	Wrong intervention
Sathianathen et al.	2023	Emergence of triplet therapy for metastatic castration-sensitive prostate cancer: An updated systematic review and network meta-analysis	Wrong comparator
Shore et al.	2024	A systematic review: Are the findings of indirect treatment comparisons (ITCs) in metastatic hormone-sensitive prostate cancer (mHSPC) consistent?	Wrong publication type (abstract)
Shore et al.	2025	Population-adjusted network meta-analyses (NMA) to evaluate the efficacy of treatment alternatives for metastatic hormone-sensitive prostate cancer (mHSPC)	Wrong publication type (abstract)
Sirisreetreerux et al.	2023	Efficacy of Treatment for Metastatic Hormone-Sensitive Prostate Cancer: An Umbrella Review of Systematic Reviews and Meta-Analyses	Wrong publication type (unbrella review)
So et al.	2020	What is the best first-line therapy for metastatic castration-sensitive prostate cancer in 2020: A network meta-analysis	Wrong publication type (abstract)
Wang et al.	2021	Cost-effectiveness of systematic treatments for metastatic castration-sensitive prostate cancer: An economic evaluation based on network meta-analysis	Wrong publication type (abstract)
Wang et al.	2022	Cost-Effectiveness of Systemic Treatments for Metastatic Castration-Sensitive Prostate Cancer: An Economic Evaluation Based on Network Meta-Analysis	Wrong outcome
Wang et al.	2023	Comparison of doublet and triplet therapies for metastatic hormone-sensitive prostate cancer: A systematic review and network meta-analysis	Wrong comparator

First author	Year	Title	Reasons for exclusion
Wang et al.	2020	CE3 Comparative effectiveness of systematic therapies for metastatic castration-sensitive prostate cancer: a parametric survival network meta-analysis of randomized controlled trials	Wrong publication type (abstract)
Wang et al.	2020	Comparative effectiveness and safety of systemic treatments for metastatic castration-sensitive prostate cancer: A parametric survival network meta-analysis of randomized controlled trials	Wrong publication type (abstract)
Wang et al.	2020	Comparative effectiveness of systemic treatments for metastatic castration-sensitive prostate cancer: A parametric survival network meta-analysis of randomized controlled trials	Wrong publication type (abstract)
Wenzel et al.	2022	Overall Survival After Systemic Treatment in High-volume Versus Low-volume Metastatic Hormone-sensitive Prostate Cancer: Systematic Review and Network Meta-analysis	Wrong outcome
Xiao et al.	2024	Efficacy and safety of androgen receptor inhibitors for treatment of advanced prostate cancer: A systematic review and network meta-analysis	Wrong population
Yanagisawa et al.	2023	Efficacy of Systemic Treatment in Prostate Cancer Patients with Visceral Metastasis: A Systematic Review, Meta-analysis, and Network Meta-analysis	Wrong population
Yanagisawa et al.	2022	Androgen Receptor Signaling Inhibitors in Addition to Docetaxel with Androgen Deprivation Therapy for Metastatic Hormone-sensitive Prostate Cancer: A Systematic Review and Meta-analysis	Wrong comparator
Yoo et al.	2023	Cost-effectiveness analysis of 7 treatments in metastatic hormone-sensitive prostate cancer: a public-payer perspective	Wrong outcome

Table 46: Full text excludes - RCT search

First author	Year	Title	Reason for exclusion
Agarwal et al.	2024	Estimating median overall survival of apalutamide compared to placebo in metastatic hormone-sensitive prostate cancer (mHSPC) populations: Statistical extrapolations of the TITAN study	Extrapolations from the final data cut in the TITAN trial
Armstrong et al.	2020	Phase 3 study of androgen deprivation therapy with enzalutamide or placebo in metastatic hormonesensitive prostate cancer: the ARCHES trial	This paper was previously included in the SLR
Azad et al.	2025	Efficacy and safety of apalutamide in metastatic castration sensitive prostate cancer patients with a prior history of cardiovascular or metabolic risk factors: A post-hoc analysis of the TITAN study	Subgroup analysis not relevant to the decision problem
Azad et al.	2025	Enzalutamide and Prostate-Specific Antigen Levels in Metastatic Prostate Cancer: A Secondary Analysis of the ARCHES Randomized Clinical Trial	Subgroup analysis not relevant to the decision problem
Bastos et al.	2025	Androgen Receptor Pathway Inhibitor Therapy for Advanced Prostate Cancer: Secondary Analysis of a Randomized Clinical Trial	Wrong drug
Chowdhury et al.	2024	Prostate-specific antigen (PSA) decline with apalutamide therapy is associated with longer survival and improved outcomes in individuals with metastatic prostate cancer: a plain language summary of the TITAN study	Subgroup analysis not relevant to the decision problem
Devos et al.	2024	Three-year oncological outcomes of the randomized phase II trial ARNEO: Neoadjuvant degarelix with or without apalutamide prior to radical prostatectomy for high-risk prostate cancer	Wrong population
Ferrario et al.	2019	Phase 3 study of androgen-deprivation therapy (ADT) with enzalutamide (ENZA) or placebo (PBO) in metastatic hormonesensitive prostate cancer (mHSPC): the ARCHES trial	Presentation slides of results from the ARCHES trial
Giesen et al.	2025	Final oncological outcomes of the randomized phase II trial ARNEO: Neoadjuvant degarelix with or without apalutamide prior to radical prostatectomy for high-risk prostate cancer	Wrong population
Merseburger et al.	2024	Apalutamide plus androgen deprivation therapy in clinical subgroups of patients with metastatic castration-sensitive prostate cancer: a subgroup analysis of the randomised clinical TITAN study	Subgroup analysis not relevant to the decision problem
Ng et al.	2024	Patient Preference of Apalutamide Versus Enzalutamide for Recurrent or Metastatic Hormone-sensitive Prostate Cancer: An Open-label, Randomized, Crossover Trial	Wrong study design
Ye et al.	2024	Patient-reported outcomes in metastatic hormone-sensitive prostate cancer (mHSPC): Results from the China ARCHES trial	Subgroup analysis not relevant to the decision problem

Table 47: Full text excludes – previous economic evaluations

First author	Year	Title	Reason for exclusion
Bencina et al.	2023	HTA and Reimbursement Status of Metastatic Hormone-Sensitive Prostate Cancer, Nonmetastatic Castration-Resistant Prostate Cancer, and Metastatic Castration-Resistant Prostate Cancer Treatments in Europe: A Patient Access Landscape Review	Wrong study design
Gedeborg et al.	2022	Time on treatment with abiraterone in men with de novo metastatic castration sensitive prostate cancer: a drug utilization study	Wrong study design
Moussa et al.	2021	A pharmacoeconomic evaluation of pharmaceutical treatment options for prostate cancer	Wrong intervention and wrong population
NICE	2021	Apalutamide with androgen deprivation therapy for treating high-risk hormone-relapsed non-metastatic prostate cancer. NICE technology appraisal guidance 740	Wrong population
NICE	2024	Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer. NICE technology appraisal guidance 951	Wrong population
Shah et al.	2022	Outcomes Following Abiraterone versus Enzalutamide for Prostate Cancer: A Scoping Review	Wrong population
Sokolova and Graff	2023	Balancing Treatment Benefits of Androgen-Receptor Signal Inhibitors and Quality of Life in Patients with Prostate Cancer	Wrong population and wrong study design
Tran and McGill	2021	Treatment Sequences of Androgen Receptor-Targeted Agents for Prostate Cancer	Wrong study design
Yang et al.	2023	Advancements in health economic evaluation research of drug treatment regimens for prostate cancer	Foreign language

Table 48: Full text excludes – literature relating to biosimilars and generics

First author	Year	Title	Reason for exclusion
Agency for Care Effectiveness	2022	Infliximab biosimilar for treating inflammatory conditions	Wrong outcome
All Wales Medicines Strategy Group	2009	Filgrastim (RatiograstimÂ®) for the treatment of neutropenia	Replacing originator - not a new indication
Aminabee et al.	2023	Pharmacoeconomic Analysis of Biologic vs. Biosimilar Therapies in Rheumatoid Arthritis	Replacing originator - not a new indication
Barker et al.	2021	Health Economic Assessment of Optimal Biological Treatment for Moderate-to-Severe Psoriasis	Replacing originator - not a new indication
Clarke et al.	2024	Modelling the opportunity for cost-savings or patient access with biosimilar adalimumab and tocilizumab: a European perspective	Replacing originator - not a new indication
Fernandez Santos et al.	2022	EE142 Cost-Effectiveness Analysis of Biosimilars Based Treatment Sequences for Moderate-to-Severe Crohn Disease in Spain	Replacing originator - not a new indication
Fernandez Santos et al.	2022	EE254 Biosimilars Impact on the Rheumatoid Arthritis Treatment: A Cost-Effectiveness Model from Spanish National Healthcare System Perspective	Replacing originator - not a new indication
Flanigan et al.	2024	Influence of clinical scenarios on costeffectiveness model results for biosimilar denosumab in women with postmenopausal osteoporosis	Wrong outcome
Hughes et al.	2019	A cost-utility analysis of biosimilar infliximab compared to reference infliximab in adult switch patients with Crohnâ€™s disease: a Canadian analysis	Replacing originator - not a new indication
Hughes et al.	2021	A Cost-Utility Analysis of Switching from Reference to Biosimilar Infliximab Compared to Maintaining Reference Infliximab in Adult Patients with Crohn's Disease	Replacing originator - not a new indication
Institute for Clinical and Economic Review	2020	Targeted Immune Modulators for Ulcerative Colitis: Effectiveness and Value. Final Evidence Report and Meeting Summary	Replacing originator - not a new indication
Lehmann et al.	2024	Determining the cost-effectiveness of follitropin alfa biosimilar compared to follitropin alfa originator in women undergoing fertility treatment in France	Replacing originator - not a new indication
Lukyanov et al.	2022	POSC152 Cost-Effectiveness Analysis of Follitropin ALFA Product (GONAL-F) Compared to Its Biosimilars Based on Meta-Analysis of Randomized Controlled Trials	Replacing originator - not a new indication
Mattli et al.	2021	Infliximab reference product versus biosimilar for the treatment of rheumatoid arthritis	Replacing originator - not a new indication
Neyt et al.	2017	Bevacizumab in the treatment of ovarian cancer	Replacing originator - not a new indication

First author	Year	Title	Reason for exclusion
Perez-Ruiz et al.	2025	Cost-effectiveness analysis of subcutaneous biosimilar tocilizumab in patients with rheumatoid arthritis in Spain	Foreign language
Perez-Ruiz et al.	2024	EE376 Rheumatoid Arthritis, Cost-Effectiveness Analysis of Biosimilar Tocilizumab in Spain	Replacing originator - not a new indication
Perez-Ruiz et al.	2024	Cost-effectiveness analysis of tocilizumab biosimilar in patients with rheumatoid arthritis in Spain	Wrong outcome
Rickard et al.	2022	Economic Evauation of Adalimumab Biosimilars and JAK Inhibitors for the Treatment of Moderate-to-Severe Rheumatoid Arthritis	Replacing originator - not a new indication
Roeder et al.	2024	Cost-Consequence Model Comparing the Originator r-hFSH-alfa and Its Biosimilar for <=4 Complete Ovarian Stimulation Cycles During Assisted Reproductive Technology Treatment in Spain, France, and Germany	Replacing originator - not a new indication
Ruggeri et al.	2021	Cost-Effectiveness Analysis of Tapentadol Versus Oxycodone/Naloxone in both Branded and Generic Formulations in Patients with Musculoskeletal Pain	Wrong intervention (not a generic or biosimilar)
Scottish Medicines Consortium	2011	filgrastim, 30 million units (300 micrograms)/0.5mL, 48 million units (480 micrograms)/0.5mL, solution for injection or infusion in pre-filled syringe (ZarzioÂ®)	Replacing originator - not a new indication
Virani et al.	2024	Efficacy, safety, and cost-effectiveness of biosimilars of bevacizumab in naive patients with diabetic macular edema	Replacing originator - not a new indication

Appendix D: NMA input data and trial baseline characteristics

ARCHES (enzalutamide with ADT versus placebo with ADT)

NMA input data

Table 49: Input data from ARCHES used in the NMAs

Outcome	Population	Follow-up, months	No. of events (% of patients)		HR	Risk of Bias
			Intervention	Control		
Trial data prior to the OLE						
rPFS	High-risk mHSPC	14.4	91 (15.9%)	201 (34.9%)	0.34 (0.25, 0.47)	SC[a]
OS	mHSPC	14.4	39 (6.7%)	45 (7.8%)	0.81 (0.53, 1.25)	Low
HRQoL[c]	mHSPC	14.4	NR	NR	0.96 (0.81, 1.14)	Low
Grade ≥3 adverse events	mHSPC	14.4	139 (24.3%)	147 (25.6%)	NA	Low
Fatigue (all grades)	mHSPC	14.4	138 (24.1%)	112 (19.5%)	NA	Low
Grade ≥ 3 Hypertension	mHSPC	14.4	19 (3.3%)	10 (1.7%)	NA	Low
Trial data after OLE						
OS	GS≥8 mHSPC	44.6 months	108 (28.0%)	145 (38.9%)	0.61 (0.48, 0.79)	High[b]
Grade ≥3 adverse events	mHSPC	44.6 months	224 (39.2%)	160 (27.9%)	NA	High[b]
Fatigue (all grades)	mHSPC	44.6 months	184 (32.2%)	118 (20.6%)	NA	High[b]
Grade ≥ 3 Hypertension	mHSPC	44.6 months	29 (5.1%)	13 (2.3%)	NA	High[b]

Abbreviations: GS, Gleason score; HR, hazard ratio; mHSPC, metastatic hormone-sensitive prostate cancer; NA, not applicable; NR, not reported; OLE open-label extension; OS, overall survival; radiological progression-free survival; SC, some concerns.

[a] Due to subgroup analysis that broke randomisation

[b] Primarily due to deviations from intended interventions

[c] Time to decrease of ≥10 points in the total Functional Assessment of Cancer Therapy–Prostate score from baseline

Participant characteristics

Table 50: Baseline characteristics of participants in ARCHES

Characteristic	Enzalutamide with ADT (n = 574)	Placebo with ADT (n = 576)
Age (years)		
Median	70.0	70.0
Range	46-92	42-92
Age category, years		
<65	148 (25.8)	152 (26.4)
65-74	256 (44.6)	255 (44.3)
≥75	170 (29.6)	169 (29.3)
Race[a]		
White	466 (81.2)	460 (79.9)
Asian	75 (13.1)	80 (13.9)
Black or African American	8 (1.4)	8 (1.4)
American Indian or Alaska Native	0	0
Native Hawaiian or other Pacific Islander	0	0
Other	2 (0.3)	3 (0.5)
Missing	23 (4.0)	25 (4.3)
Geographic region		
Europe	341 (59.4)	344 (59.7)
Asia-Pacific	104 (18.1)	113 (19.6)
North America	86 (15.0)	77 (13.4)
South America	32 (5.6)	30 (5.2)
Other	11 (1.9)	12 (2.1)
ECOG performance status score on day 1		
0	448 (78.0)	443 (76.9)
1	125 (21.8)	133 (23.1)
Total Gleason score at initial diagnosis		
<8	171 (29.8)	187 (32.5)
≥8	386 (67.2)	373 (64.8)
Confirmed metastases at screening[b]		
Yes	536 (93.4)	531 (92.2)
No	34 (5.9)	45 (7.8)
Unknown	4 (0.7)	0
Localization of confirmed metastases at screening[b]		
Bone only	268 (46.7)	245 (42.5)
Soft tissue only	51 (8.9)	45 (7.8)
Bone and soft tissue	217 (37.8)	241 (41.8)
Distant metastasis at initial diagnosis		

Characteristic	Enzalutamide with ADT (n = 574)	Placebo with ADT (n = 576)
M1	402 (70.0)	365 (63.4)
M0	83 (14.5)	86 (14.9)
MX/Unknown	88 (15.3)	125 (21.7)
Disease volume		
High[c]	354 (61.7)	373 (64.8)
Low	220 (38.3)	203 (35.2)
Prior local therapy		
Radical prostatectomy	72 (12.5)	89 (15.5)
Radiation therapy	73 (12.7)	72 (12.5)
No. of cycles of prior docetaxel chemotherapy		
0	471 (82.1)	474 (82.3)
1-5	14 (2.4)	11 (1.9)
6	89 (15.5)	91 (15.8)
Previous use of ADT[d]		
None	39 (6.8)	61 (10.6)
≤3 months	414 (72.1)	394 (68.4)
>3 months	121 (21.1)	120 (20.8)
Unknown[e]	0	1 (0.2)
Median duration of prior ADT, months (range)[f]	1.6 (0.03-55.3)	1.6 (0.03-198.8)
Previous use of antiandrogen[g]	205 (35.8)	229 (39.9)
Median PSA, ng/mL (range)[g]	5.4 (0-4,823.5)	5.1 (0-19,000.0)
Modified QLQ-PR25 urinary symptoms score, mean (SD)[h]	35.2 (25.3)	35.8 (25.4)
FACT-P total score, mean (SD)[i]	113.9 (19.8)	112.7 (19.0)
BPI-SF item 3 (worst pain), mean (SD)[j]	1.8 (2.4)	1.8 (2.3)
BPI-SF pain severity score, mean (SD)[j]	1.4 (1.8)	1.4 (1.7)

Abbreviations: ADT, androgen deprivation therapy; BPI-SF, Brief Pain Inventory – Short Form; ECOG, Eastern Cooperative Oncology Group; FACT-P, Functional Assessment of Cancer Therapy – Prostate; M1, distant metastasis; PSA, Prostate-Specific Antigen.

[a] By country regulations, race is not collected in France.

[b] Assessed by independent central review after investigator assessment at study entry.

[c] Defined by CHAARTED criteria6 as presence of metastases involving the viscera, or, in the absence of visceral lesions, four or more bone lesions, one or more of which must be in a bony structure beyond the vertebral column and pelvic bone; some study sites incorrectly reported disease volume information for some patients at the time of randomization, which was corrected during medical review on study entry, resulting in a difference of approximately 20 patients with either high or low disease volume between the treatment arms

[d] Includes the time since bilateral orchiectomy for patients who had prior bilateral orchiectomy.

[e] The patient had prior ADT; however, the duration of ADT use was unknown.

[f] Intent-to-treat patients who had received prior ADT (enzalutamide with ADT, n = 535; placebo with ADT, n = 514).

[g] Safety-analysis-set patients (enzalutamide with ADT, n = 572; placebo with ADT, n = 574).

[h] Intent-to-treat patients who had a baseline modified QLQ-PR25 urinary symptoms score (enzalutamide with ADT, n = 539; placebo with ADT, n = 546). Only items Q31-Q33 from the urinary symptoms subscale were assessed. All items and scale scores of the QLQ-PR25 are linearly transformed to a 0 to 100 scale. A higher score in the urinary symptoms subscale indicates more symptoms.

[i] Intent-to-treat patients who had a baseline Functional Assessment of Cancer Therapy–Prostate total score (enzalutamide with ADT, n = 550; placebo with ADT, n = 553). The Functional Assessment of Cancer Therapy–Prostate total score ranges from 0 to 156, with the higher scores indicating more favorable quality of life.

[j] Intent-to-treat patients who had baseline average Brief Pain Inventory–Short Form worst pain and pain severity scores (enzalutamide with ADT, n = 542; placebo

LATITUDE (abiraterone with ADT versus placebo with ADT)

NMA input data

Table 51: Input data from LATITUDE used in the NMAs

Outcome	Population	Follow-up, months	No. of events (% of patients)		HR	Risk of Bias
			Intervention	Control		
Trial data prior to the OLE						
rPFS	High-risk mHSPC	30.4	239 (40%)	354 (59%)	0.47 (0.39, 0.55)	Low
OS	High-risk mHSPC	30.4	169 (28%)	237 (39%)	0.62 (0.51, 0.76)	Low
HRQoL[b]	High-risk mHSPC	30.4	347 (58.1%)	369 (61.3%)	0.85 (0.74,0.99)	Low
Grade ≥3 adverse events	High-risk mHSPC	30.4	374 (62.6%)	287 (47.7%)	NA	Low
Fatigue (all grades)	High-risk mHSPC	30.4	77 (12.9%)	86 (14.3%)	NA	Low
Grade ≥ 3 Hypertension	High-risk mHSPC	30.4	121 (20.3%)	59 (9.8%)	NA	Low
Trial data after OLE						
OS	High-risk mHSPC	51.8	275 (46.1%)	343 (57.0%)	0.66 (0.56, 0.78)	High[a]
Grade ≥3 adverse events	High-risk mHSPC	51.8	403 (67.5%)	299 (49.7%)	NA	High[a]
Fatigue (all grades)	High-risk mHSPC	51.8	84 (14.0%)	90 (15.0%)	NA	High[a]
Grade ≥ 3 Hypertension	High-risk mHSPC	51.8	125 (20.9%)	60 (10.0%)	NA	High[a]

Abbreviations: HR, hazard ratio; mHSPC, metastatic hormone-sensitive prostate cancer; NA, not applicable; OLE open-label extension; OS, overall survival; rPFS, radiological progression-free survival.

[a] Primarily due to deviations from intended interventions

[b] Time to decrease of ≥10 points in the total Functional Assessment of Cancer Therapy–Prostate score from baseline

Participant characteristics

Table 52: Baseline characteristics of participants in LATITUDE

	AAP + ADT (n=597)	ADT Alone (n=602)
Age, median years (range)	68 (38–89)	67 (33–92)
Median PSA level before ADT, ng/mL (range)	25.4 (0–8,775.9)	23.1 (0.1–8,889.6)
ECOG PS, n (%)	0: 326 (54.6) 1: 245 (41.0) 2: 26 (4.4)	0: 331 (55.0) 1: 255 (42.4) 2: 16 (2.7)
Gleason score at initial diagnosis, n (%)	<7: 4 (0.7) 7: 9 (2) ≥8: 584 (98)	<7: 1 (0.2) 7: 15 (2) ≥8: 586 (97)
Baseline pain score (BPI-SF Item 3), n (%)	N: 570 0–1: 284 (50) 2–3: 123 (22) ≥4: 163 (29)	N: 579 0–1: 288 (50) 2–3: 137 (24) ≥4: 154 (27)
≥3 bone metastases at screening, n (%)	586 (98.2)	585 (97.2)
High-risk at screening, n (%)	597 (100)	601 (100)
Gleason score ≥8 + ≥3 bone lesions	573 (96)	569 (95)
Gleason score ≥8 + measurable visceral disease	82 (14)	87 (14)
≥3 bone lesions + measurable visceral disease	84 (14)	85 (14)
Gleason score ≥8 + ≥3 bone lesions + measurable visceral disease	71 (12)	70 (12)
Extent of disease, n (%)	596 (100)	600 (100)
Bone	580 (97)	585 (98)
Liver	32 (5)	30 (5)
Lungs	73 (12)	72 (12)
Node	283 (47)	287 (48)
Prostate mass	151 (25)	154 (26)
Viscera	18 (3)	13 (2)
Soft Tissue	9 (2)	15 (3)
Other	2 (0.3)	0
Bone lesions at screening, n (%)		
0	6 (1.0)	7 (1.2)
1–2	5 (0.8)	10 (1.7)
3–10	202 (33.8)	208 (34.6)
11–20	109 (18.3)	97 (16.1)
>20	275 (46.1)	280 (46.5)
Previous prostate cancer therapy, n (%)	560 (94)	560 (93)
Radiotherapy	19 (3)	26 (4)

	AAP + ADT (n=597)	**ADT Alone (n=602)**
Hormonal	559 (96)	558 (93)
GnRH agonists/antagonists[a]	449 (75)	450 (75)
Orchidectomy[a]	73 (12)	71 (12)
First-generation androgen receptor agonists	373 (62)	371 (62)
Other	7 (1)	10 (2)
Time from GnRH agonist/antagonist to first dose of study drug, median months (range)	1.08 (0.1–3.0)	1.08 (0.1–3.5)
[Post-hoc] High-volume disease, n (%)	487 (81.5)	468 (77.7)

Abberviations: AAP, abiraterone acetate + prednisolone; ADT, androgen deprivation therapy; BPI-SF, Brief Pain Inventory – Short Form; ECOG, Eastern Cooperative Oncology Group; GnRH, gonadotropin-releasing hormone; ITT, intention-to-treat; PS, performance status; PSA, prostate specific antigen.

[a] within 3 months prior to randomisation.

STAMPEDE (abiraterone with ADT versus ADT)

NMA input data

Table 53: Input data from STAMPEDE used in the NMAs

Outcome	Population	Follow-up, months	No. of events (% of patients)		HR	Risk of Bias
			Intervention	Control		
Trial data after median 40 months follow-up						
rPFS	High-risk mHSPC	40	198 (21%)	379 (39%)	0.46 (0.36, 0.59)	High[a]
OS	High-risk mHSPC	40	184 (19%)	262 (27%)	0.54 (0.41, 0.7)	SC[b]
Grade ≥3 adverse events	HSPC	40	443 (46.7%)	315 (32.8%)	NA	SC[c]
Fatigue (all grades)	HSPC	40	648 (68.4%)	551 (57.4%)	NA	SC[c]
Grade ≥ 3 Hypertension	mHSPC	96	44 (4.6%)	13 (1.4%)	NA	SC[b]
Trial data after 96 months follow-up						
OS	mHSPC	96	290 (57.9%)	370 (73.7%)	0.62 (0.53, 0.73)	SC[b]
Grade ≥3 adverse events	mHSPC	96	271 (54.4%)	192 (38.2%)	NA	SC[b]
Fatigue (all grades)	mHSPC	96	272 (54.1)	342 (68.7%)	NA	SC[b]
Grade ≥ 3 Hypertension	mHSPC	96	26 (5.2%)	6 (1.2%)	NA	SC[b]

Abbreviations: HR, hazard ratio; mHSPC, metastatic hormone-sensitive prostate cancer; NA, not applicable; OS, overall survival; rPFS, radiological progression-free survival; SC, some concerns.

[a] Primarily because the measured outcome was PFS rather than rPFS

[b] Due to subgroup analysis that broke randomisation

[c] Due to differences in population to that specified in the protocol

Participant characteristics

Table 54: Baseline characteristics of HSPC participants in STAMPEDE

Characteristic	Abiraterone with ADT (N=960)	ADT Alone (N=957)
Age at randomization — yr		
Median (IQR)	67 (63 to 72)	67 (62 to 72)
Range	42 to 85	39 to 84
PSA level before ADT — ng/ml		
Median (IQR)	51 (19 to 158)	56 (19 to 165)

Characteristic	Abiraterone with ADT (N=960)	ADT Alone (N=957)
Range	0 to 21,460	0 to 10,530
WHO performance status — no. (%)[a]		
0	745 (78)	744 (78)
1 or 2	215 (22)	213 (22)
Disease group — no. (%)		
Newly diagnosed node-negative, nonmetastatic disease	253 (26)	256 (27)
Newly diagnosed node-positive, nonmetastatic disease	182 (19)	187 (20)
Newly diagnosed metastatic disease	465 (48)	476 (50)
Previously treated nonmetastatic disease	25 (3)	12 (1)
Previously treated metastatic disease	35 (4)	26 (3)
Gleason score — no. (%)[b]		
≤7	221 (23)	223 (23)
8 to 10	715 (74)	721 (75)
Unknown	24 (2)	13 (1)
Planned or current long-term ADT — no. (%)		
Orchiectomy	3 (<1)	5 (1)
Bicalutamide	5 (1)	5 (1)
Dual androgen blockade	1 (<1)	4 (<1)
LHRH-based[c]	951 (99)	943 (99)
Time to initiation of ADT from randomization — days[d]		
Median (IQR)	−44 (−63 to −24)	−45 (−67 to −23)
Range	−85 to 28	−85 to 39
Planned antiandrogen use — no. (%)		
No	61 (6)	50 (5)
Short-term antiandrogen	895 (93)	902 (94)
Long-term antiandrogen	4 (<1)	5 (1)
Radiotherapy planned — no. (%)[e]		
Yes	564 (59)	561 (59)
No	396 (41)	396 (41)
Hypertension — no. (%)		
No	557 (58)	571 (60)
Yes, but still fit for trial	401 (42)	385 (40)
Cardiovascular assessment not received	2 (<1)	1 (<1)

Abbreviations: ADT, androgen deprivation therapy; IQR, interquartile range; LHRH, Luteinizing Hormone-Releasing Hormone; PSA, Prostate-Specific Antigen; WHO, World Health Organization.

[a] The World Health Organization (WHO) performance status was scored on a scale of 0 to 4, with higher numbers indicating greater disability.

[b] Gleason scores range from 3 to 10, with higher scores indicating more aggressive disease, less differentiated tumor, and worse prognosis.

[c] All patients with planned use of luteinizing hormone–releasing hormone (LHRH) analogues should have antiandrogens for disease flares, at least.

[d] Data were missing for one patient in the ADT-alone group.

[e] Radiotherapy was mandated for patients with newly diagnosed node-negative, nonmetastatic disease and strongly encouraged in patients with newly diagnosed node-positive, nonmetastatic disease.

Table 55: Baseline characteristics of mHSPC participants in STAMPEDE

Characteristic	Combination Therapy (N=501)	ADT Alone (N=502)
Age, years		
Median (IQR)	67 (62–71)	67 (62–72)
Range	42–85	39–84
PSA level before ADT — ng/ml		
Median (IQR)	96 (29–371)	97 (26–358)
Range	0–21460	1–10530
WHO performance status — no. (%)[a]		
0	376 (75%)	370 (74%)
1	118 (24%)	125 (25%)
2	7 (1%)	7 (1%)
T stage[b]		
T0–T2	51 (10%)	56 (11%)
T3	289 (58%)	270 (54%)
T4	118 (24%)	137 (27%)
Tx	43 (9%)	39 (8%)
Gleason score — no. (%)[c]		
≤7	115 (23%)	118 (24%)
8	117 (23%)	106 (21%)
9	231 (46%)	245 (49%)
10	18 (4%)	23 (5%)
Unknown	20 (4%)	10 (2%)
N stage (pelvic nodes)		
N0	167 (33%)	175 (35%)
N+	293 (58%)	291 (58%)
NX	41 (8%)	36 (7%)
Time to initiation of ADT from randomization — days		
Median (IQR)	77 (54–97)	71 (51–95)
Range	3–5384	0–4866
Metastatic volume		
Low	222 (44%)	204 (41%)
High	253 (51%)	271 (54%)
Missing	26 (5%)	27 (5%)
Pain from prostate cancer		
Absent	389 (78%)	396 (79%)
Present	107 (21%)	102 (20%)

Characteristic	Combination Therapy (N=501)	ADT Alone (N=502)
Unknown	5 (1%)	4 (1%)
Aspirin use		
No	411 (82%)	412 (82%)
Yes	90 (18%)	90 (18%)
Non-steroidal anti-inflammatory drug use		
No	449 (90%)	448 (89%)
Yes	52 (10%)	54 (11%)
Planned or current hormone therapy		
Orchiectomy	3 (1%)	3 (1%)
Luteinising hormone-releasing hormone agonists or antagonists	498 (99%)	497 (99%)
Bicalutamide	0	1 (<1%)
Maximum androgen blockade	0	1 (<1%)
Palliative radiotherapy planned as standard of care		
No	480 (96%)	479 (95%)
Yes	21 (4%)	23 (5%)
Previous treatment to prostate		
No	466 (93%)	475 (95%)
Yes	35 (7%)	27 (5%)
Docetaxel planned as standard of care		
No	0	0
Yes	0	0
Not applicable (before change in standard of care)	501 (100%)	502 (100%)

ADT, androgen deprivation therapy; IQR, interquartile range; PSA, Prostate-Specific Antigen; WHO, World Health Organization.

[a] The World Health Organization (WHO) performance status was scored on a scale of 0 to 4, with higher numbers indicating greater disability.

[b] The "T" stage in prostate cancer staging refers to the primary tumour's size and extent within the prostate gland. higher T stages (T3 and T4) indicate a greater extent of tumour growth outside the prostate gland, suggesting a more advanced stage of the disease.

[c] Gleason scores range from 3 to 10, with higher scores indicating more aggressive disease, less differentiated tumor, and worse prognosis

Table 56: Baseline characteristics of high-risk mHSPC participants in STAMPEDE

Characteristic	Abiraterone with ADT (N=241)	ADT Alone (N=232)
Age at randomization — yr		
Median (IQR)	67 (63–71)	67 (63–72)
PSA level before ADT — ng/ml		
Median (IQR)	126 (36–458)	174 (40–735)
WHO performance status — no. (%)[a]		
0	163	177

Characteristic	Abiraterone with ADT (N=241)	ADT Alone (N=232)
1 or 2	69	64
Gleason score — no. (%)[b]		
≤7	2	2
8 to 10	239	229
T stage[b]		
T0–T2	21	23
T3	141	116
T4	59	68
Tx	20	25
Regional node status		
N1	84	78
N+	131	137
NX	26	17
Eligibility		
M+, new	238	229
Previously treated	3	3
Metastatic site		
Node	-	-
Bone	169	154
Visceral	-	1
Bone + node	52	60
Bone + visceral	12	9
Visceral + node	1	1
Bone + node + visceral	7	7

Abbreviations: ADT, androgen deprivation therapy; IQR, interquartile range; LHRH, Luteinizing Hormone-Releasing Hormone; PSA, Prostate-Specific Antigen; WHO, World Health Organization.

[a] The World Health Organization (WHO) performance status was scored on a scale of 0 to 4, with higher numbers indicating greater disability.

[b] Gleason scores range from 3 to 10, with higher scores indicating more aggressive disease, less differentiated tumor, and worse prognosis.

TITAN (apalutamide with ADT versus placebo with ADT)

NMA input data

Table 57: Input data from TITAN used in the NMAs

Outcome	Population	Follow-up, months	No. of events (% of patients)		HR	Risk of Bias
			Intervention	Control		
Trial data prior to the OLE						
rPFS	GS≥8 mHSPC	22.7	167 (31.8%)	277 (52.5%)	0.48 (0.37, 0.61)	Low
OS	GS≥8 mHSPC	22.7	83 (16%)	117 (22%)	0.73 (0.52, 1.01)	Low
Grade ≥3 adverse events	mHSPC	22.7	221 (42.2%)	215 (40.8%)	NA	Low
Fatigue (all grades)	mHSPC	22.7	103 (19.7%)	88 (16.7%)	NA	Low
Grade ≥ 3 Hypertension	mHSPC	22.7	44 (8.4%)	48 (9.1%)	NA	Low
Trial data after OLE						
OS	High-risk mHSPC	44.0	112 (38.8%)	160 (55.9%)	0.57 (0.45, 0.73)	High[a]
Grade ≥3 adverse events	mHSPC	44.0	259 (49.4%)	220 (41.7%)	NA	High[a]
Fatigue (all grades)	mHSPC	44.0	107 (20.4%)	89 (16.9%)	NA	High[a]

Abbreviations: GS, Gleason score; HR, hazard ratio; mHSPC, metastatic hormone-sensitive prostate cancer; NA, not applicable; OLE open-label extension; OS, overall survival; rPFS, radiological progression-free survival.
[a] Primarily due to deviations from intended interventions

Participant characteristics

Table 58: Baseline characteristics of mHSPC participants in TITAN

	Apalutamide with ADT (n = 525)	Placebo with ADT (n = 527)	Total (n = 1052)
Demographics			
Age	(n=525)	(n=527)	(n=1052)
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Age categorisation, n (%)			
<65	[redacted]	[redacted]	[redacted]
65-69	[redacted]	[redacted]	[redacted]
70-74	[redacted]	[redacted]	[redacted]
≥ 75	[redacted]	[redacted]	[redacted]

	Apalutamide with ADT (n = 525)	**Placebo with ADT (n = 527)**	**Total (n = 1052)**
Race, n (%)	(n=525)	(n=527)	(n=1052)
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)	(n=525)	(n=525)	(n=1052)
Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Weight, kg, n	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Height, cm	(n=519)	(n=524)	(n=1043)
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Disease characteristics			
Time from initial diagnosis to randomization (months)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Time from metastatic diagnosis to randomization (months)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Metastasis stage at diagnosis, n (%)			
M0	[redacted]	[redacted]	[redacted]
M1	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Gleason score at initial diagnosis, n (%)			
< 7	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
BPI-SF Pain Score, n [b]	(n=503)	(n=513)	(n=1016)
Mean (SD)	[redacted]	[redacted]	[redacted]
Median range)	[redacted]	[redacted]	[redacted]
ECOG PS, n (%)			

	Apalutamide with ADT (n = 525)	**Placebo with ADT (n = 527)**	**Total (n = 1052)**
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
Prior docetaxel use			
No	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
Extent of disease at study entry, n (%)			
Bone	[redacted]	[redacted]	[redacted]
Bone only	[redacted]	[redacted]	[redacted]
Lymph node	[redacted]	[redacted]	[redacted]
Visceral	[redacted]	[redacted]	[redacted]
Lung	[redacted]	[redacted]	[redacted]
Liver	[redacted]	[redacted]	[redacted]
Soft tissue	[redacted]	[redacted]	[redacted]
Number of bone lesions at study entry, n (%)			
≤ 10	[redacted]	[redacted]	[redacted]
> 10	[redacted]	[redacted]	[redacted]
Subgroups of mHSPC[c], n (%)			
High volume	[redacted]	[redacted]	[redacted]
Low volume	[redacted]	[redacted]	[redacted]
Previous prostate cancer therapy, n (%)			
Prostatectomy or radiotherapy	[redacted]	[redacted]	[redacted]
Prostatectomy only	[redacted]	[redacted]	[redacted]
Radiotherapy only	[redacted]	[redacted]	[redacted]
Both prostatectomy and radiotherapy	[redacted]	[redacted]	[redacted]
Hormone therapy	[redacted]	[redacted]	[redacted]
First generation anti-androgen	[redacted]	[redacted]	[redacted]
GnRHa	[redacted]	[redacted]	[redacted]
Bilateral Orchiectomy	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]
Vandetanib	[redacted]	[redacted]	[redacted]

Abbreviations: ADT, androgen deprivation therapy; BPI-SF, Brief Pain Inventory Short Form; ECOG, Eastern Cooperative Oncology Group; GnRHa, gonadotropin releasing hormone analogue; M0, primary progressor; M1, newly diagnosed; Mhspc, metastatic hormone-sensitive prostate cancer.

[a] Time from initial diagnosis in months is defined from the date initial diagnosis to the date of randomisation +1 divided by 30.4375. Time from metastatic diagnosis in weeks is defined from the date of metastatic diagnosis to the date of randomisation +1 divided by 7;

[b] based on the average of a maximum of the 7 records closest to the first dose using a window of 14 days prior with minimum of 1 day;

[c] high-volume mHSPC is defined as 1) visceral metastases and at least 1 bone lesion or 2) at least 4 bone lesions, with at least 1 bone lesion outside of the vertebral column or pelvis. Low volume mHSPC is defined as the presence of bone lesion(s) not meeting the definition of high-volume mHSPC.

Appendix E: Testing the proportional hazards assumption

This appendix presents the results that were used to determine whether the assumption that hazard functions were proportional between treatment groups was appropriate for the outcomes of rPFS and OS in each of the main studies of interest.

rPFS

LATITUDE

Results based on digitising the KM curves that appear in Figure 1 of Fizazi et al. (2017).[16]

Figure 9: Non-parametric estimate of the logarithm of the hazard ratio function (solid line) with 95% confidence bounds (dashed lines) for LATITUDE rPFS data

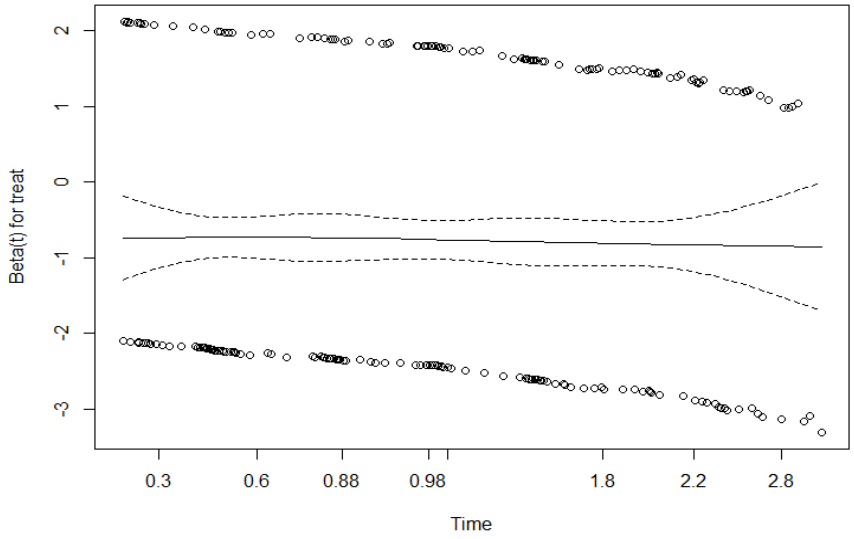
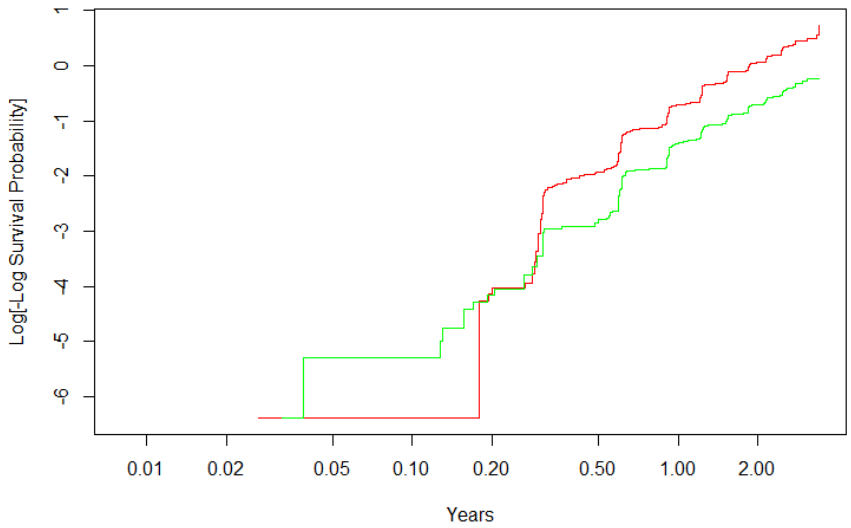


Figure 10: Log cumulative hazard plot for LATITUDE rPFS data



Chi-squared test statistic for the correlation of the Schoenfeld residuals over time:

0.176 (p=0.67)

STAMPEDE

Results based on digitising the KM curves that appear in Supplement Figure 2B (High risk patients) of Hoyle et al. (2019).[19]

Figure 11: Non-parametric estimate of the logarithm of the hazard ratio function (solid line) with 95% confidence bounds (dashed lines) for STAMPEDE PFS data

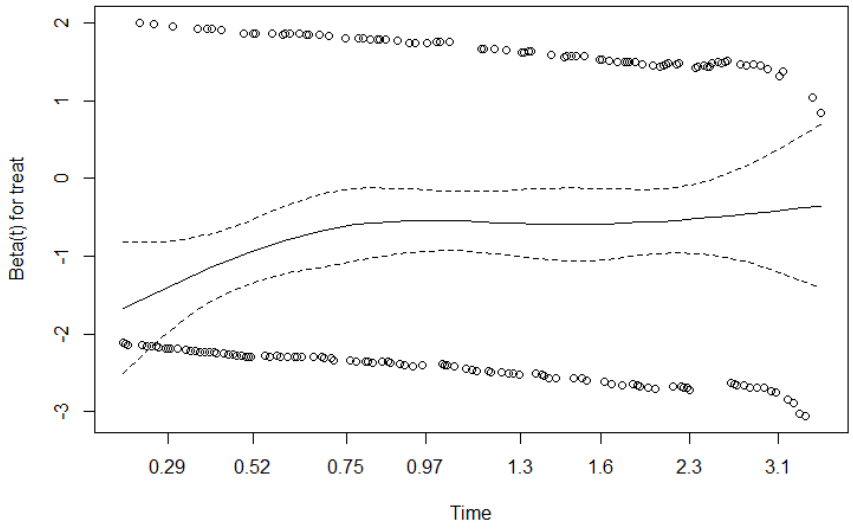
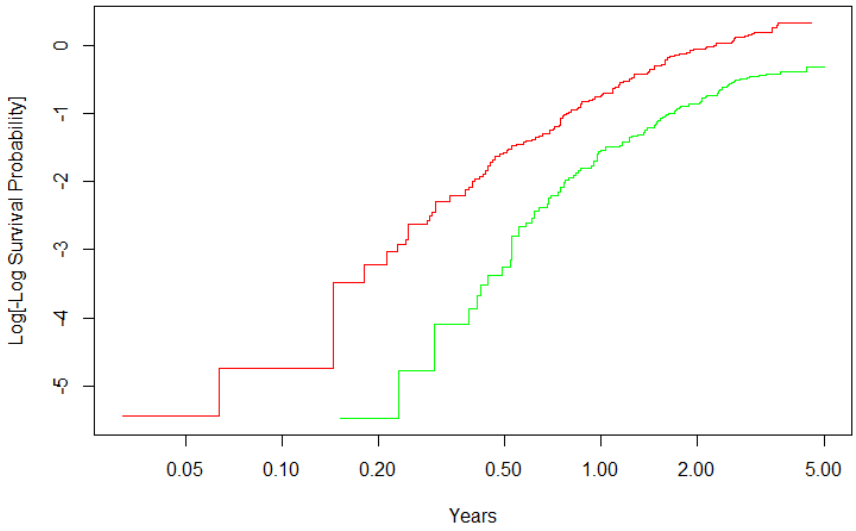


Figure 12: Log cumulative hazard plot for STAMPEDE PFS data



Chi-squared test statistic for the correlation of the Schoenfeld residuals over time: 4.32 (p=0.038)

TITAN

Results based on digitising the KM curves that appear in Figure 1 of Chi at al. (2019).[21]

Figure 13: Non-parametric estimate of the logarithm of the hazard ratio function (solid line) with 95% confidence bounds (dashed lines) for TITAN rPFS data

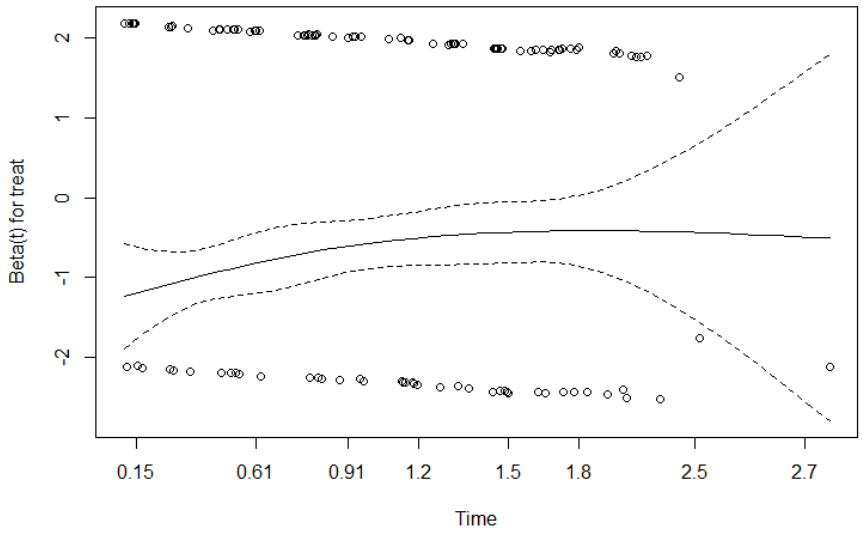
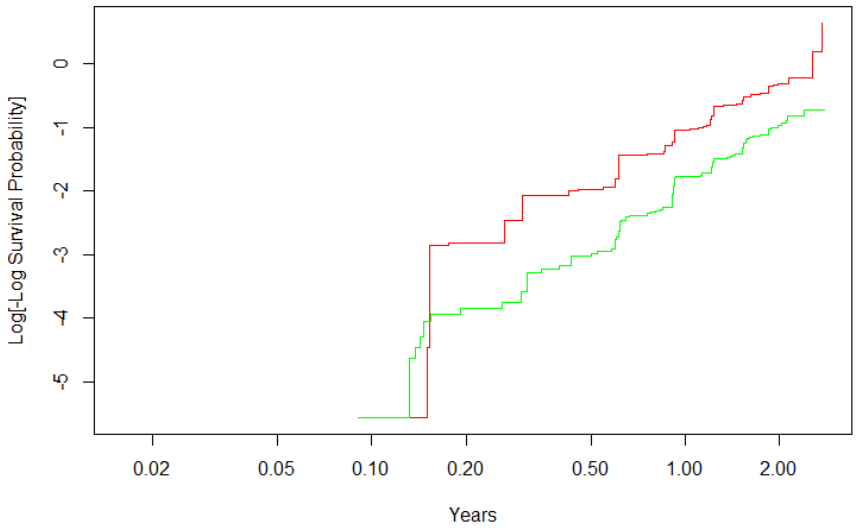


Figure 14: Log cumulative hazard plot for TITAN rPFS data



Chi-squared test statistic for the correlation of the Schoenfeld residuals over time:

5.09 (p=0.024)

ARCHES

Results based on digitising the KM curves that appear in Supplementary Figure 2b (people with high-risk mHSPC) of Azad et al. (2022).[78]

Figure 15: Non-parametric estimate of the logarithm of the hazard ratio function (solid line) with 95% confidence bounds (dashed lines) for ARCHES rPFS data :

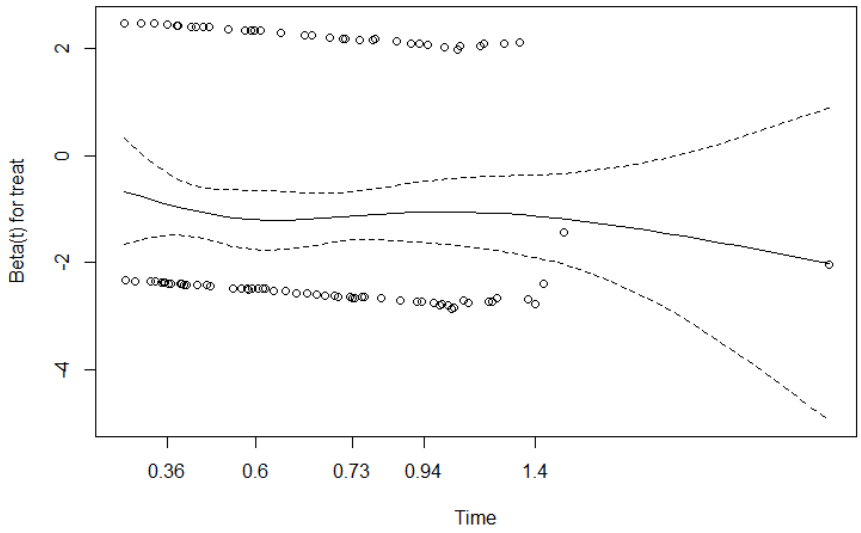
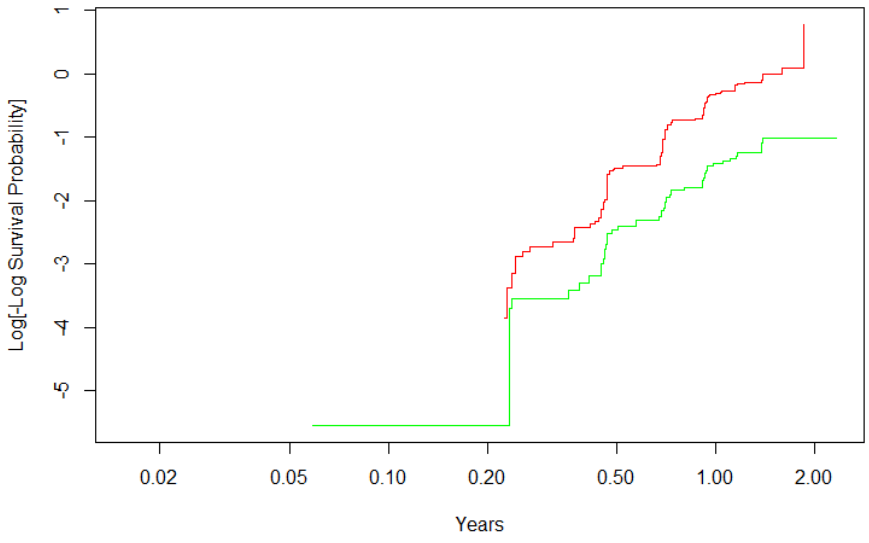


Figure 16: Log cumulative hazard plot for ARCHES rPFS data



Chi-squared test statistic for the correlation of the Schoenfeld residuals over time: 0.43 (p=0.51)

OS

LATITUDE

Results based on digitising the KM curves that appear in Figure 1 of Fizazi et al. (2017).[16]

Figure 17: Non-parametric estimate of the logarithm of the hazard ratio function (solid line) with 95% confidence bounds (dashed lines) for LATITUDE OS data:

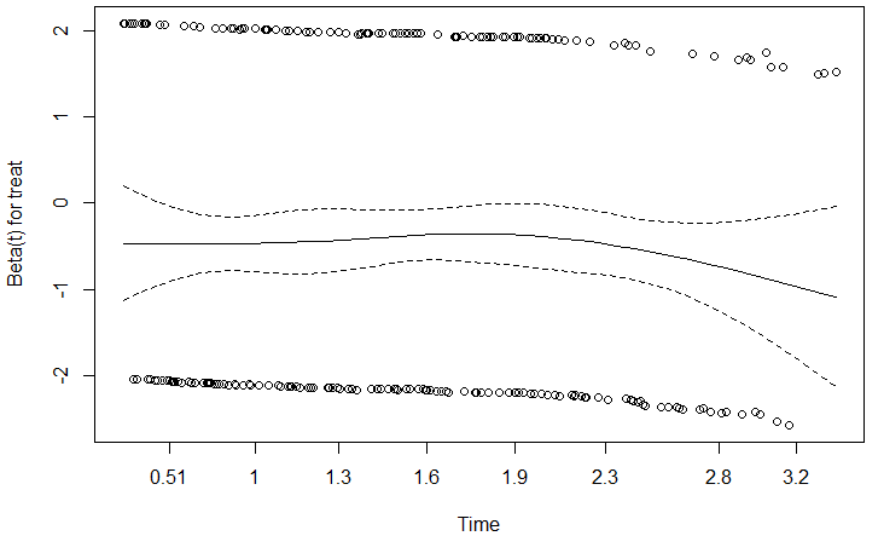
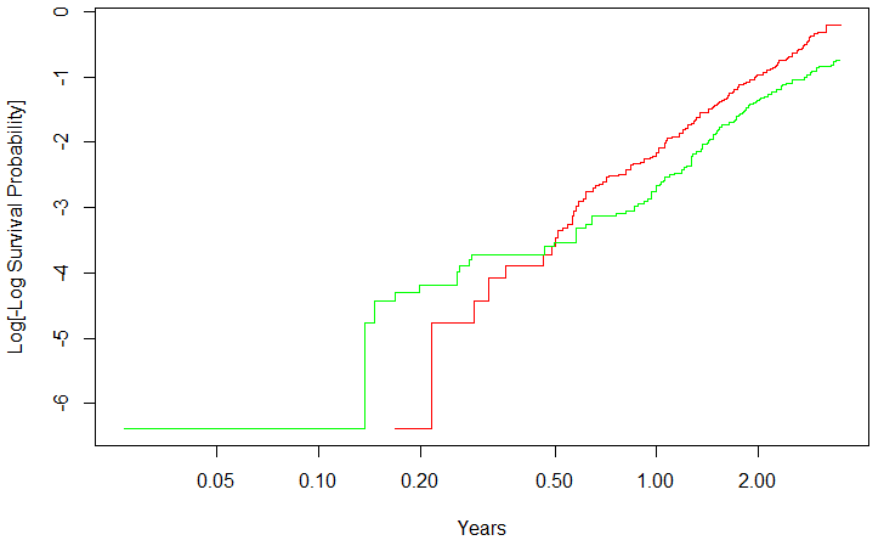


Figure 18: Log cumulative hazard plot for LATITUDE OS data:



Chi-squared test statistic for the correlation of the Schoenfeld residuals over time:

0.313 (0.58)

STAMPEDE

Results based on digitising the KM curves that appear in Figure 2B (High risk patients) of Hoyle at al. (2019).[19]

Figure 19: Non-parametric estimate of the logarithm of the hazard ratio function (solid line) with 95% confidence bounds (dashed lines) for STAMPEDE OS data:

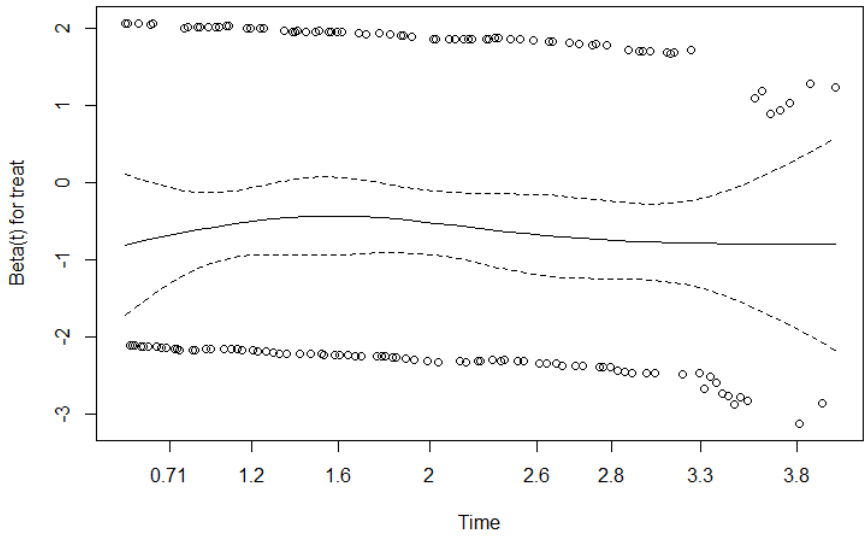
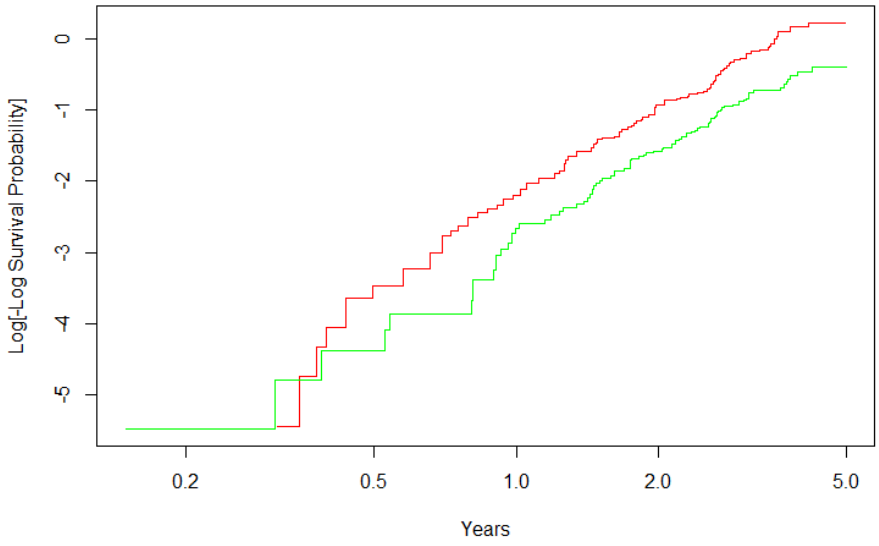


Figure 20: Log cumulative hazard plot for STAMPEDE OS data:



Chi-squared test statistic for the correlation of the Schoenfeld residuals over time:
0.21 (p=0.65)

TITAN

Results based on digitising the KM curves that appear in Figure 2 of Chi at al. (2019).[21]

Figure 21: Non-parametric estimate of the logarithm of the hazard ratio function (solid line) with 95% confidence bounds (dashed lines) for TITAN OS data:

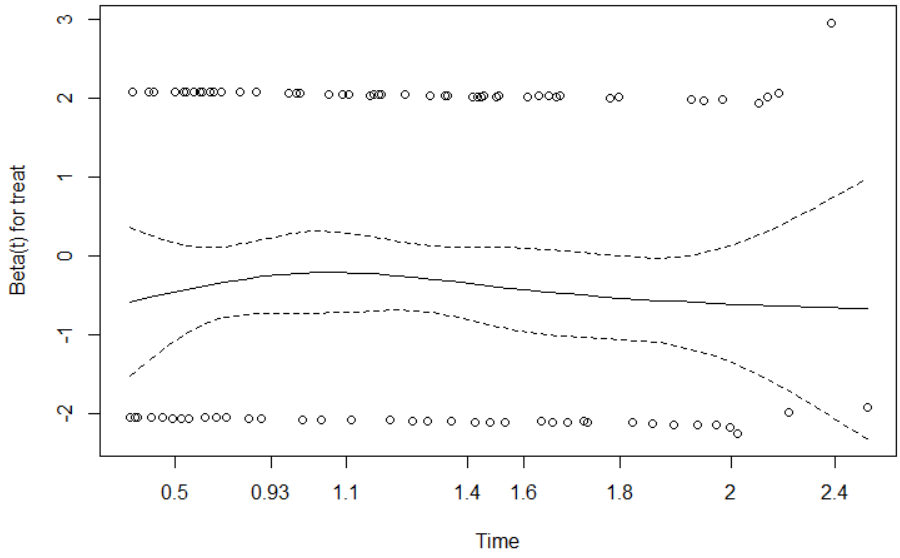
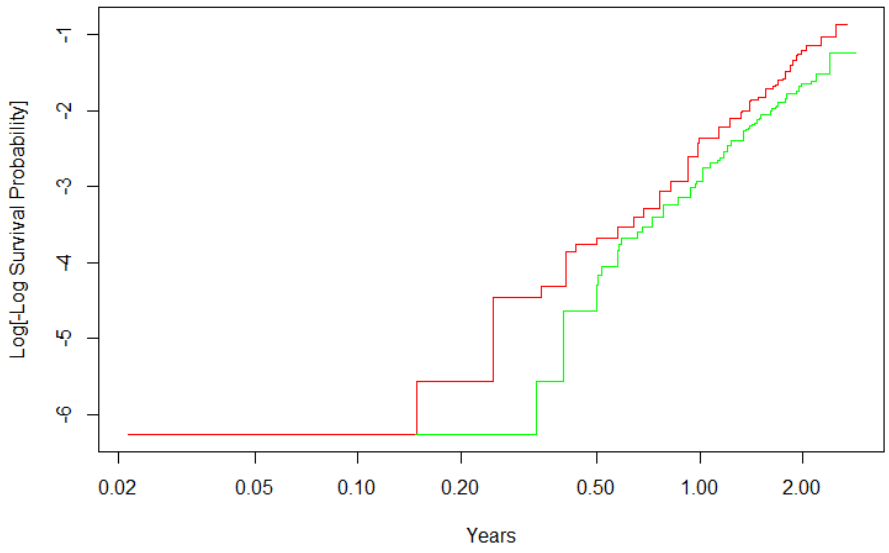


Figure 22: Log cumulative hazard plot for TITAN OS data:



Chi-squared test statistic for the correlation of the Schoenfeld residuals over time:

0.232 (p=0.63)

ARCHES

Results based on digitising the KM curves that appear in Supplementary Figure A2 of Armstrong at al. (2019).[15]

Figure 23: Non-parametric estimate of the logarithm of the hazard ratio function (solid line) with 95% confidence bounds (dashed lines) for ARCHES OS data :

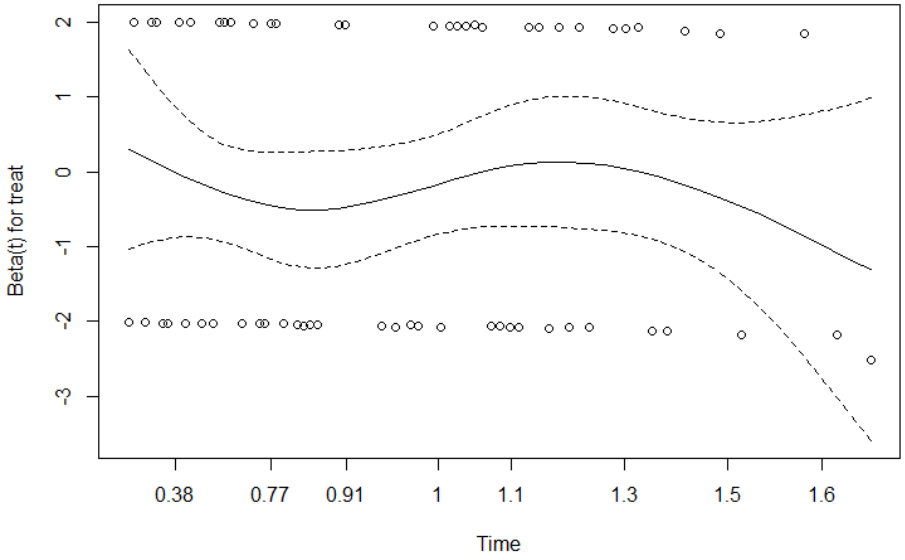
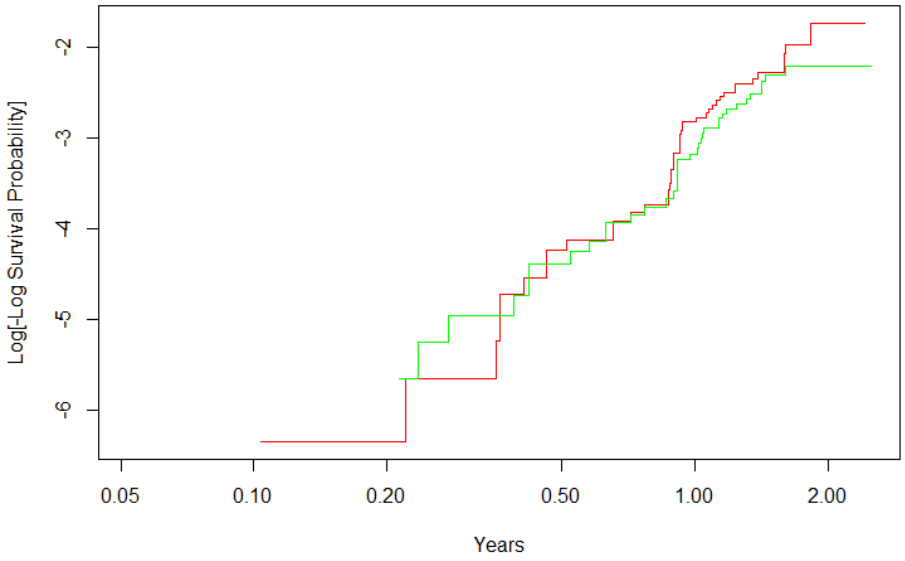


Figure 24: Log cumulative hazard plot for ARCHES OS data



Chi-squared test statistic for the correlation of the Schoenfeld residuals over time: 0.0724 (p=0.79)

Appendix F: NMA sensitivity analyses

This appendix contains additional information concerning the results of the main NMAs of outcomes of interest that were outlined in Section 5.3 and the results of sensitivity analyses of these main analyses that were conducted according to the criteria detailed in the (Methods) Section 5.2.3

rPFS

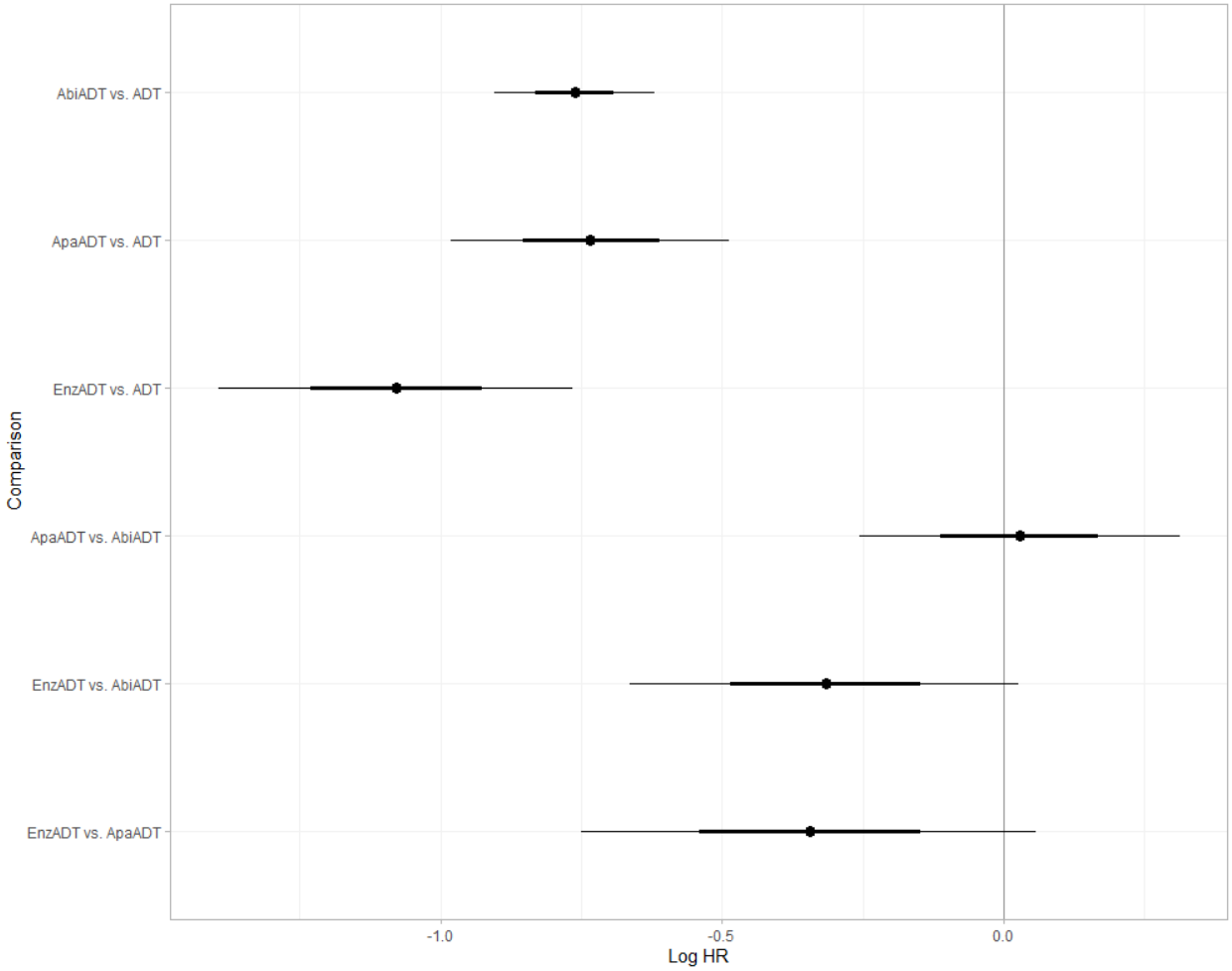
Main analysis of latest trial data up to a 40 month follow-up

Included studies (populations):

- LATITUDE (people with high-risk mHSPC)
- TITAN (people with mHSPC who have a Gleason Score ≥ 8)
- ARCHES (people with high-risk mHSPC)
- STAMPEDE (people with high-risk mHSPC)

Outcome: Hazard ratio (HR) of radiographic progression-free survival (rPFS)
Statistical method: Fixed effect network meta-analysis under the assumption of proportional hazard functions.

Figure 25: Forest plot of rPFS NMA results in terms of the logarithm of HR



Bullets are point estimates. Regular lines are 95% credible intervals. Bold lines are point estimates ± one standard deviation.
Abbreviations: ADT, ADT only; AbiADT, Abiraterone with ADT; ApaADT, Apalutamide with ADT, EnzADT, Enzalutamide with ADT.

Table 59: Estimates of Log HR for treatment comparisons of interest:

Comparison	Log HR	sd	95% CrIs of Log HR	
AbiADT vs. ADT	-0.76	0.07	-0.90	-0.62
ApaADT vs. ADT	-0.73	0.13	-0.98	-0.49
EnzADT vs. ADT	-1.08	0.16	-1.39	-0.77
ApaADT vs. AbiADT	0.03	0.15	-0.26	0.31
EnzADT vs. AbiADT	-0.32	0.18	-0.66	0.03
EnzADT vs. ApaADT	-0.34	0.21	-0.75	0.06

Abbreviations: sd, standard deviation; CrIs, credible intervals.

Table 60: Estimates of HR with 95% credible intervals

	Abi + ADT	**Enz + ADT**	**Apa + ADT**	**ADT**
Abi + ADT	-	1.37 (0.97, 1.94)	0.97 (0.73, 1.29)	0.47 (0.41, 0.54)
Enz + ADT	0.73 (0.51,1.03)	-	0.71 (0.47, 1.06)	0.34 (0.25, 0.46)
Apa + ADT	1.03 (0.77, 1.37)	1.41 (0.94, 2.12)	-	0.48 (0.37, 0.61)
ADT	2.14 (1.86, 2.47)	2.94 (2.15, 4.03)	2.08 (1.63, 2.67)	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide.

Note: The comparison is the row-forming treatment against the column-forming treatment.

Sensitivity check of main analysis of latest trial data up to a 40 month follow-up

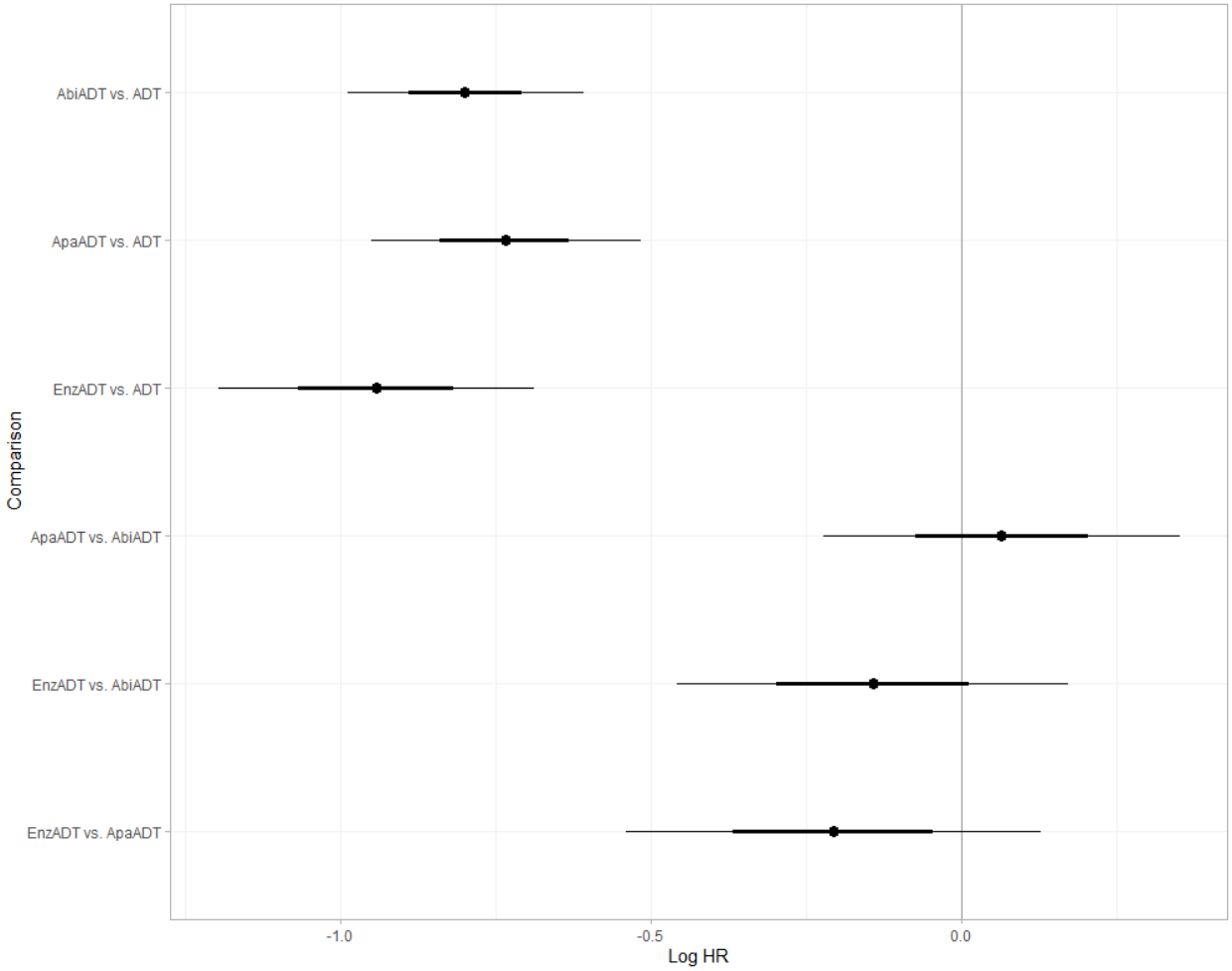
Following the methodology outlined in Section 5.2.3, a sensitivity analysis was performed of the main NMA for rPFS that was just presented that included trial data relating to rPFS for all mHSPC patients in the trials of interest independent of risk classification rather than focusing on people with high-risk mHSPC. It can be seen that the results of the main NMA for rPFS are not highly sensitive to the risk classification of the patients.

Included studies (populations):

- TITAN (people with mHSPC)
- ARCHES (people with mHSPC)
- STAMPEDE (people with mHSPC)

Outcome: HR of overall survival
Statistical method: Fixed effect network meta-analysis under the assumption of proportional hazard functions.

Figure 26: Forest plot of rPFS sensitivity analysis results in terms of the logarithm of HR:



Bullets are point estimates. Regular lines are 95% credible intervals. Bold lines are point estimates ± one standard deviation.
Abbreviations: ADT, ADT only; AbiADT, Abiraterone with ADT; ApaADT, Apalutamide with ADT; EnzADT, Enzalutamide with ADT.

Table 61: Estimates of Log HR for treatment comparisons of interest:

Comparison	Log HR	sd	95% CrIs of Log HR	
AbiADT vs. ADT	-0.80	0.10	-0.99	-0.61
ApaADT vs. ADT	-0.73	0.11	-0.95	-0.52
EnzADT vs. ADT	-0.94	0.13	-1.20	-0.69
ApaADT vs. AbiADT	0.06	0.15	-0.22	0.35
EnzADT vs. AbiADT	-0.14	0.16	-0.46	0.17
EnzADT vs. ApaADT	-0.21	0.17	-0.54	0.13

Abbreviations: sd, standard deviation; CrIs, credible intervals.

Table 62: Estimates of HR for rPFS with 95% credible intervals:

	Abi + ADT	**Enz + ADT**	**Apa + ADT**	**ADT**
Abi + ADT	-	1.15 (0.84, 1.58)	0.94 (0.70, 1.25)	0.45 (0.37, 0.54)
Enz + ADT	0.87 (0.63, 1.19)	-	0.81 (0.58, 1.13)	0.39 (0.30, 0.50)
Apa + ADT	1.07 (0.80, 1.42)	1.23 (0.88, 1.71)	-	0.48 (0.39, 0.60)
ADT	2.22 (1.84, 2.68)	2.56 (1.99, 3.31)	2.08 (1.68, 2.58)	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

OS

Main analysis of latest trial data up to a 40 month follow-up

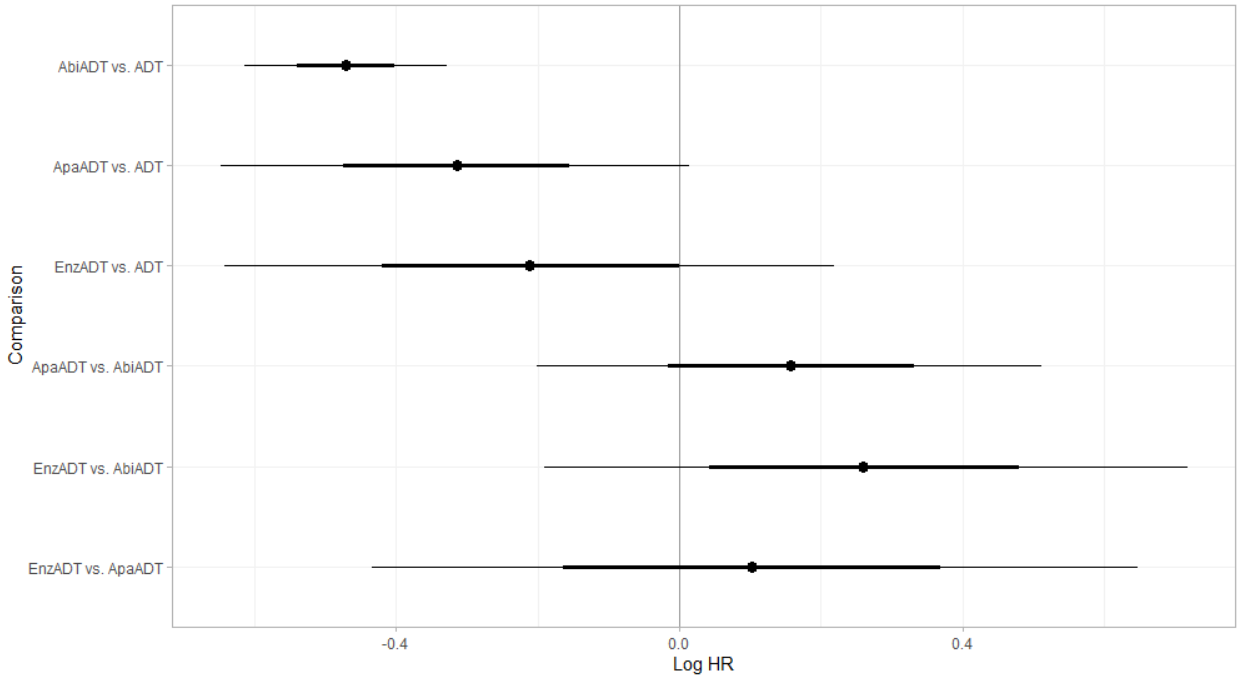
Included studies (population subgroups):

- LATITUDE (people with high-risk mHSPC)
- TITAN (people with mHSPC and a Gleason Score ≥ 8)
- ARCHES (people with mHSPC)
- STAMPEDE (people with high-risk mHSPC)

Outcome: HR of overall survival

Statistical method: Fixed effect network meta-analysis under the assumption of proportional hazard functions.

Figure 27: Forest plot of OS NMA results in terms of the logarithm of HR:



Bullets are point estimates. Regular lines are 95% credible intervals. Bold lines are point estimates ± one standard deviation.
Abbreviations: ADT, ADT only; AbiADT, Abiraterone with ADT; ApaADT, Apalutamide with ADT; EnzADT, Enzalutamide with ADT.

Table 63: Estimates of Log HR for treatment comparisons of interest:

Comparison	Log HR	sd	95% CrIs of Log HR	
AbiADT vs. ADT	-0.47	0.07	-0.61	-0.33
ApaADT vs. ADT	-0.31	0.17	-0.65	0.01
EnzADT vs. ADT	-0.21	0.22	-0.64	0.22
ApaADT vs. AbiADT	0.16	0.18	-0.20	0.51
EnzADT vs. AbiADT	0.26	0.23	-0.19	0.72
EnzADT vs. ApaADT	0.10	0.28	-0.43	0.65

Abbreviations: sd, standard deviation; CrIs, credible intervals.

Table 64: Estimates of HR for OS with 95% credible intervals:

	Abi + ADT	**Enz + ADT**	**Apa + ADT**	**ADT**
Abi + ADT	-	0.77 (0.49, 1.21)	0.85 (0.60, 1.22)	0.62 (0.54, 0.72)
Enz + ADT	1.30 (0.83, 2.05)	-	1.11 (0.65, 1.91)	0.81 (0.53, 1.24)
Apa + ADT	1.17 (0.82, 1.67)	0.90 (0.52, 1.54)	-	0.73 (0.52,1.01)
ADT	1.60 (1.39, 1.85)	1.23 (0.80, 1.90)	1.37 (0.99, 1.91)	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

Main analysis of latest trial data after unblinding

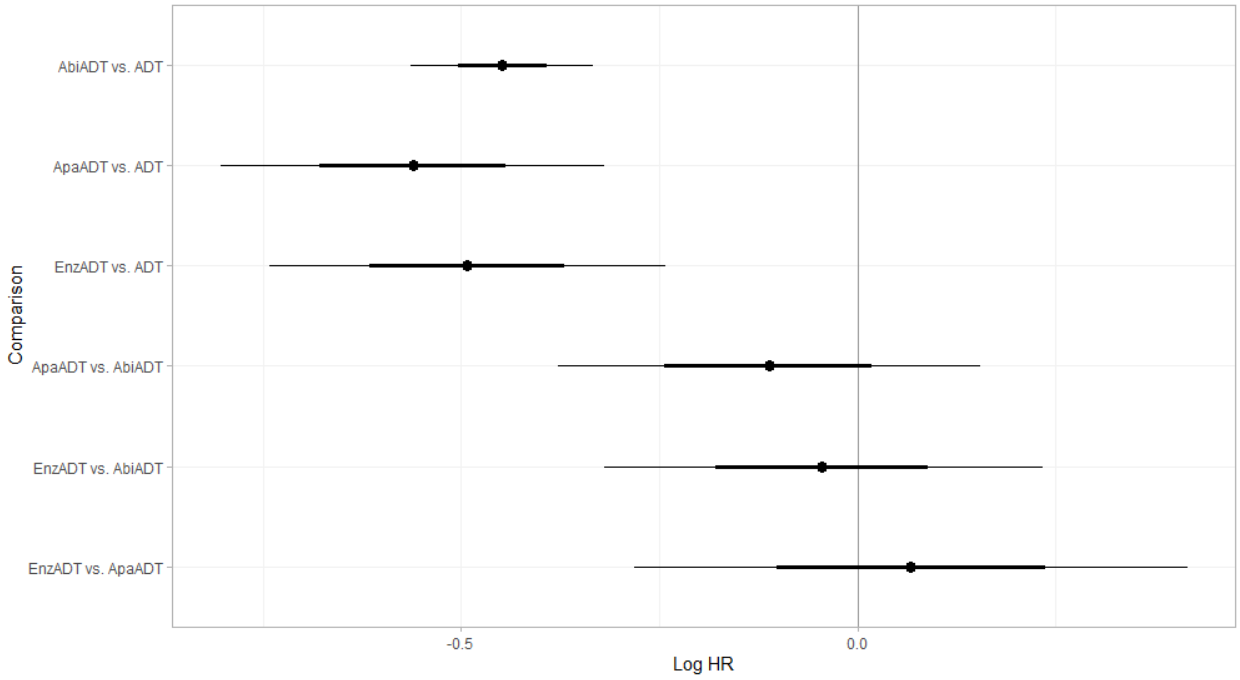
Included studies (populations):

- LATITUDE (people with high-risk mHSPC)
- TITAN (people with high-risk mHSPC)
- ARCHES (people with mHSPC and a Gleason Score ≥ 8)
- STAMPEDE (people with mHSPC)

Outcome: HR of overall survival

Statistical method: Fixed effect network meta-analysis under the assumption of proportional hazard functions.

Figure 28: Forest plot of NMA OS results in terms of the logarithm of HR:



Bullets are point estimates. Regular lines are 95% credible intervals. Bold lines are point estimates ± one standard deviation.
Abbreviations: ADT, ADT only; AbiADT, Abiraterone with ADT; ApaADT, Apalutamide with ADT; EnzADT, Enzalutamide with ADT.

Table 65: Estimates of Log HR for treatment comparisons of interest

Comparison	Log HR	sd	95% CrIs of Log HR	
AbiADT vs. ADT	-0.45	0.06	-0.56	-0.33
ApaADT vs. ADT	-0.56	0.12	-0.80	-0.32
EnzADT vs. ADT	-0.49	0.13	-0.74	-0.24
ApaADT vs. AbiADT	-0.11	0.14	-0.38	0.15
EnzADT vs. AbiADT	-0.05	0.14	-0.32	0.23
EnzADT vs. ApaADT	0.07	0.18	-0.28	0.42

Abbreviations: sd, standard deviation; CrIs, credible intervals.

Table 66: Estimates of HR for OS with 95% credible intervals

	Abi + ADT	**Enz + ADT**	**Apa + ADT**	**ADT**
Abi + ADT	-	1.05 (0.79, 1.38)	1.12 (0.86, 1.46)	0.64 (0.57, 0.72)
Enz + ADT	0.96 (0.73, 1.26)	-	1.07 (0.75, 1.52)	0.61 (0.48 0.78)
Apa + ADT	0.89 (0.69, 1.17)	0.93 (0.66, 1.33)	-	0.57 (0.45 0.73)
ADT	1.57 (1.39, 1.76)	1.64 (1.27, 2.10)	1.57 (1.39, 1.76)	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

Sensitivity check of main analysis of latest trial data up to a 40 month follow-up

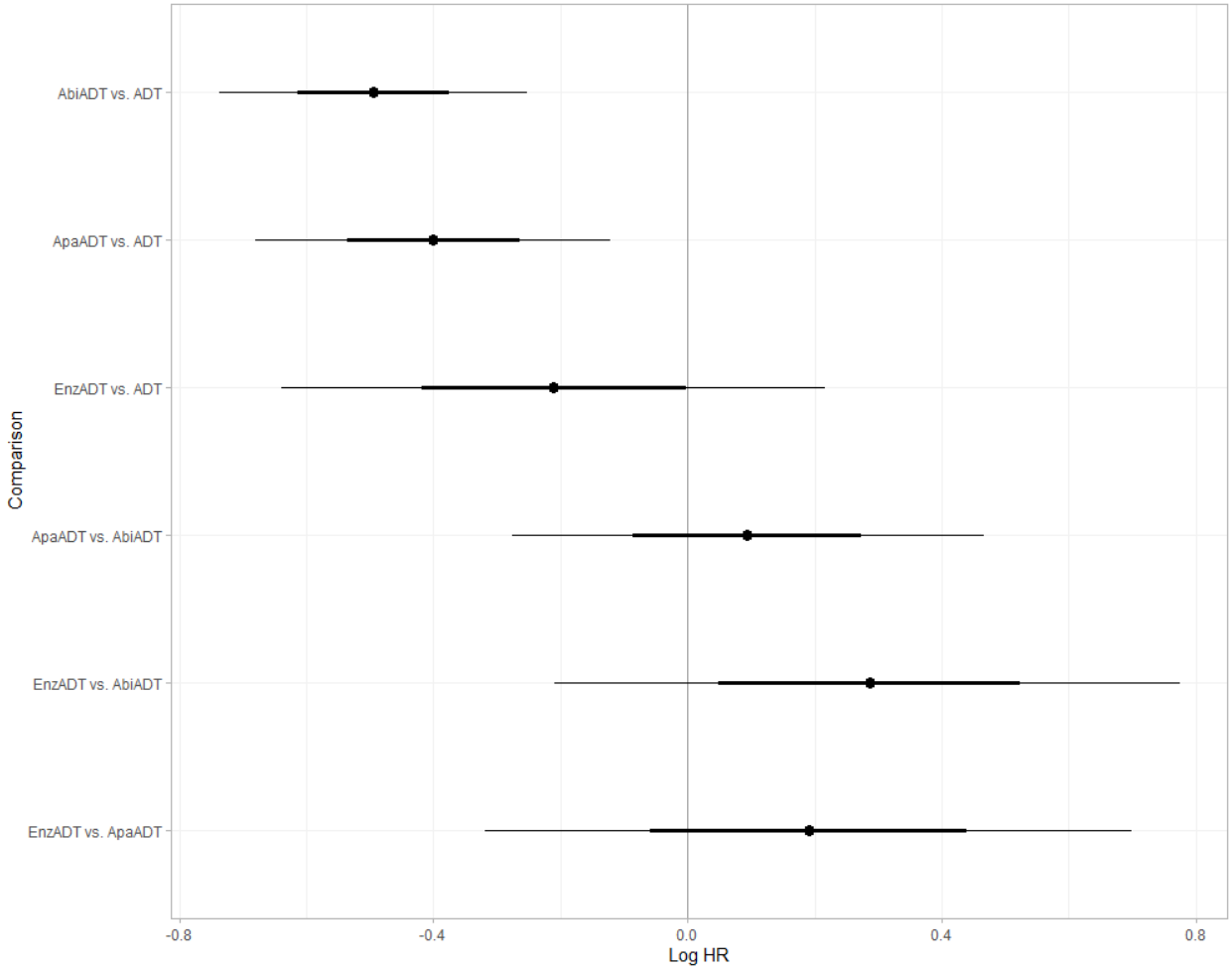
Following the methodology outlined in Section 5.2.3, a sensitivity analysis was performed of the NMA just presented for the latest trial data up to a 40 month follow-up that included trial data relating to OS for all mHSPC patients in the trials of interest independent of risk classification rather than focusing on high risk mHSPC patients. It can be seen that the results of the NMA for OS for the latest trial data up to a 40 month follow-up are not highly sensitive to the risk classification of the patients.

Included studies (populations):

- TITAN (people with mHSPC)
- ARCHES (people with mHSPC)
- STAMPEDE (people with mHSPC)

Outcome: HR of overall survival
Statistical method: Fixed effect network meta-analysis under the assumption of proportional hazard functions.

Figure 29: Forest plot of NMA OS results in terms of the logarithm of HR:



Bullets are point estimates. Regular lines are 95% credible intervals. Bold lines are point estimates ± one standard deviation.

Abbreviations: ADT, ADT only; AbiADT, Abiraterone with ADT; ApaADT, Apalutamide with ADT; EnzADT, Enzalutamide with ADT.

Table 67: Estimates of Log HR for treatment comparisons of interest:

Comparison	Log HR	sd	95% CrIs of Log HR	
AbiADT vs. ADT	-0.49	0.12	-0.74	-0.25
ApaADT vs. ADT	-0.40	0.14	-0.68	-0.12
EnzADT vs. ADT	-0.21	0.22	-0.64	0.22
ApaADT vs. AbiADT	0.09	0.19	-0.28	0.47
EnzADT vs. AbiADT	0.28	0.25	-0.21	0.77
EnzADT vs. ApaADT	0.19	0.26	-0.32	0.70

Abbreviations: sd, standard deviation; CrIs, credible intervals.

Table 68: Estimates of HR for OS with 95% credible intervals

	Abi + ADT	**Enz + ADT**	**Apa + ADT**	**ADT**
Abi + ADT	-	0.75 (0.46, 1.23)	0.91 (0.63, 1.32)	0.61 (0.48, 0.78)
Enz + ADT	1.33 (0.81, 2.17)	-	1.21 (0.73, 2.01)	0.81 (0.53, 1.24)
Apa + ADT	1.10 (0.76, 1.60)	0.83 (0.50, 1.37)	-	0.67 (0.51, 0.88)
ADT	1.64 (1.29, 2.09)	1.23 (0.80, 1.89)	1.49 (1.13, 1.97)	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

Sensitivity check of main analysis of latest trial data after unblinding

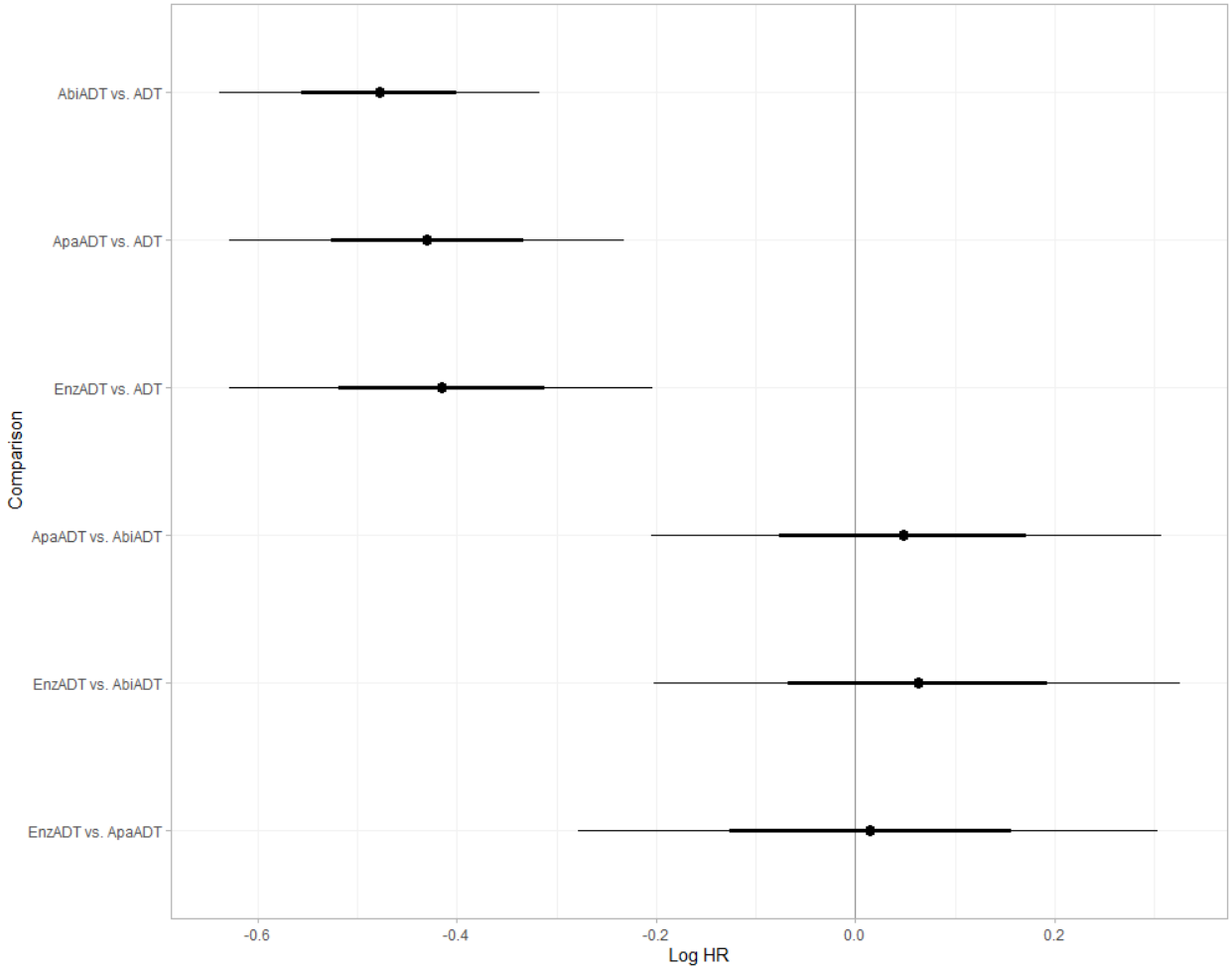
A sensitivity analysis was performed of the NMA just presented for the latest trial data after the trials concerned became open label that included trial data relating to OS for all mHSPC patients in the trials of interest independent of risk classification rather than focusing on high risk mHSPC patients. It can be seen that the results of the NMA for OS for the latest trial data after unblinding are not highly sensitive to the risk classification of the patients.

Included studies (populations):

- TITAN (people with mHSPC)
- ARCHES (people with mHSPC)
- STAMPEDE (people with mHSPC)

Outcome: HR of overall survival
Statistical method: Fixed effect network meta-analysis under the assumption of proportional hazard functions.

Figure 30: Forest plot of NMA OS results in terms of the logarithm of HR:



Bullets are point estimates. Regular lines are 95% credible intervals. Bold lines are point estimates ± one standard deviation.

Abbreviations: ADT, ADT only; AbiADT, Abiraterone with ADT; ApaADT, Apalutamide with ADT; EnzADT, Enzalutamide with ADT.

Table 69: Estimates of Log HR for treatment comparisons of interest:

Comparison	Log HR	sd	95% CrIs of Log HR	
AbiADT vs. ADT	-0.48	0.08	-0.64	-0.32
ApaADT vs. ADT	-0.43	0.10	-0.63	-0.23
EnzADT vs. ADT	-0.42	0.11	-0.63	-0.20
ApaADT vs. AbiADT	0.05	0.13	-0.21	0.31
EnzADT vs. AbiADT	0.06	0.14	-0.20	0.33
EnzADT vs. ApaADT	0.01	0.15	-0.28	0.30

Abbreviations: sd, standard deviation; CrIs, credible intervals.

Table 70: Estimates of HR for OS with 95% credible intervals

	Abi + ADT	**Enz + ADT**	**Apa + ADT**	**ADT**
Abi + ADT	-	0.94 (0.72, 1.22)	0.95 (0.74, 1.23)	0.62 0.53 0.73
Enz + ADT	1.06 (0.82, 1.38)	-	1.01 (0.76, 1.35)	0.66 0.53 0.82
Apa + ADT	1.05 (0.81, 1.36)	0.99 (0.74, 1.32)	-	0.65 0.53 0.79
ADT	1.61 (1.37, 1.89)	1.52 (1.23, 1.88)	1.54 (1.26, 1.88)	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

HRQoL

Analysis of latest trial data up to a 40-month follow-up

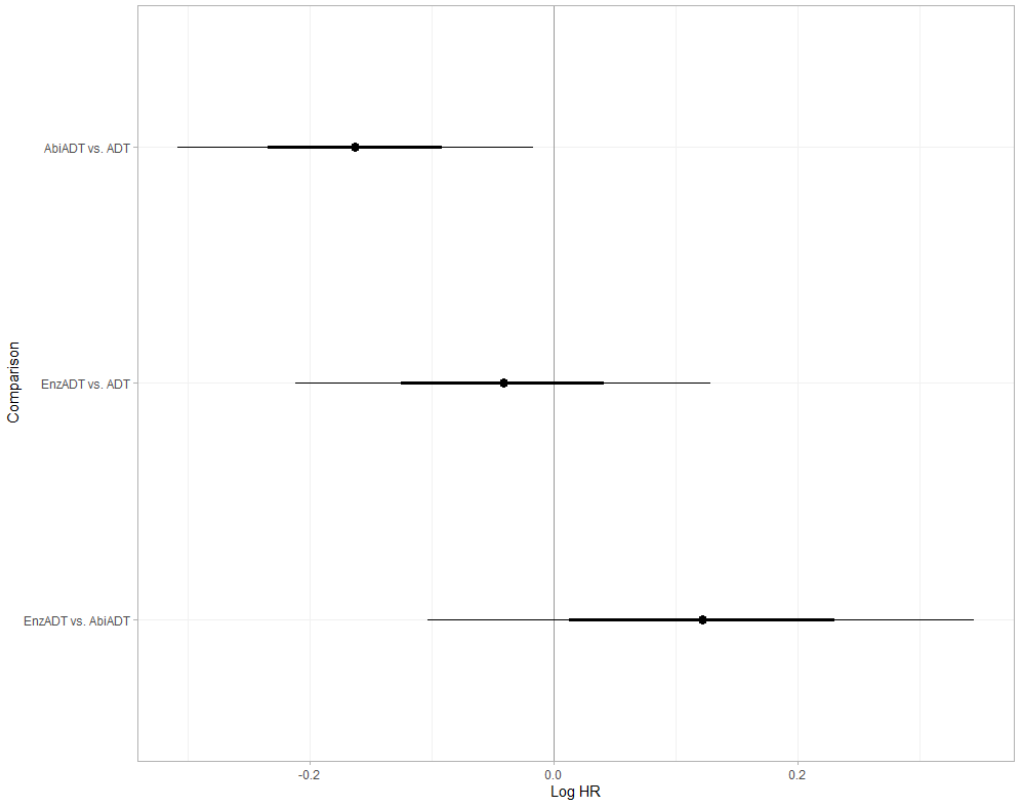
Included studies (populations):

- LATITUDE (People with high-risk mHSPC)
- ARCHES (People with mHSPC)

Outcome: HR of time to deterioration of quality of life (QoL). Deterioration of QoL was defined as a decrease of ≥10 points in the total Functional Assessment of Cancer Therapy–Prostate score from baseline.

Statistical method: Fixed effect network meta-analysis under the assumption of proportional hazard functions.

Figure 31: Forest plot of NMA results in terms of the logarithm of HR:



Bullets are point estimates. Regular lines are 95% credible intervals. Bold lines are point estimates ± one standard deviation.

Abbreviations: ADT, ADT only; AbiADT, Abiraterone with ADT; ApaADT, EnzADT, Enzalutamide with ADT.

Table 71: Estimates of Log HR for treatment comparisons of interest:

Comparison	Log HR	sd	95% CrIs of Log HR	
AbiADT vs. ADT	-0.16	0.07	-0.31	-0.02
EnzADT vs. ADT	-0.04	0.09	-0.21	0.13
EnzADT vs. AbiADT	0.12	0.11	-0.10	0.34

Abbreviations: sd, standard deviation; CrIs, credible intervals.

Table 72: Estimates of HR for time to deterioration of HRQoL with 95% credible intervals

	Abi + ADT	**Enz + ADT**	**ADT**
Abi + ADT	-	0.89 (0.71, 1.11)	0.85 (0.73, 0.98)
Enz + ADT	1.13 (0.90, 1.41)	-	0.96 (0.81, 1.14)
ADT	1.18 (1.02, 1.36)	1.04 (0.88, 1.24)	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

Sensitivity check of main analysis of latest trial data up to a 40-month follow-up

This sensitivity check could not be performed according to the criteria outlined in Section 5.2.3 due to lack of relevant trial data.

Grade 3 or 4 adverse events

Main analysis of latest trial data up to a 40-month follow-up

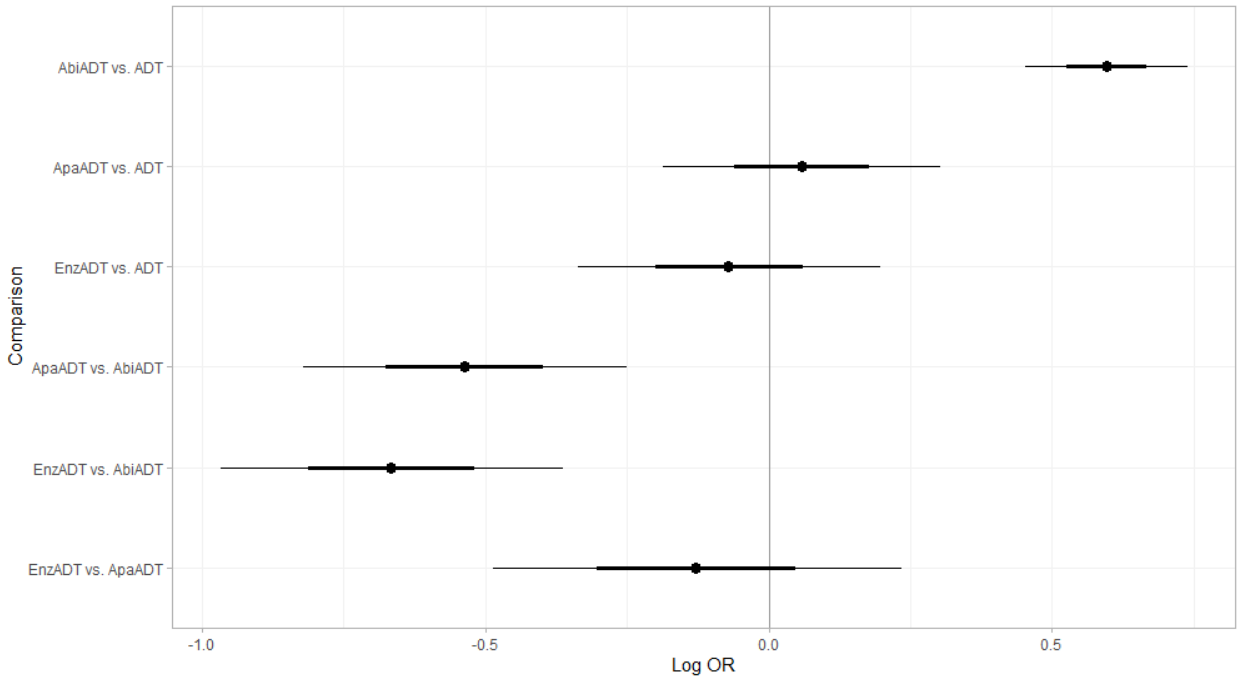
Included studies (populations):

- LATITUDE (People with high-risk mHSPC)
- TITAN (People with mHSPC)
- ARCHES (People with mHSPC)
- STAMPEDE (People with mHSPC)

Outcome: Odds ratio (OR) of a grade 3 or 4 adverse event

Statistical method: Fixed effect network meta-analysis

Figure 32: Forest plot of NMA Grade 3 or 4 adverse events results in terms of the logarithm of OR:



Bullets are point estimates. Regular lines are 95% credible intervals. Bold lines are point estimates ± one standard deviation.

Abbreviations: ADT, ADT only; AbiADT, Abiraterone with ADT; ApaADT, Apalutamide with ADT; EnzADT, Enzalutamide with ADT.

Table 73: Estimates of Log OR for treatment comparisons of interest

Comparison	Log OR	sd	95% CrIs of Log OR	
AbiADT vs. ADT	0.60	0.07	0.45	0.74
ApaADT vs. ADT	0.06	0.13	-0.19	0.30
EnzADT vs. ADT	-0.07	0.14	-0.34	0.20
ApaADT vs. AbiADT	-0.54	0.15	-0.82	-0.25
EnzADT vs. AbiADT	-0.67	0.15	-0.97	-0.36
EnzADT vs. ApaADT	-0.13	0.18	-0.49	0.24

Abbreviations: sd, standard deviation; CrIs, credible intervals.

Table 74: Estimates of OR for grade 3 or 4 adverse events with 95% credible intervals

	Abi + ADT	**Enz + ADT**	**Apa + ADT**	**ADT**
Abi + ADT	-	1.95 (1.44, 2.63)	1.71 (1.29, 2.27)	1.81 (1.57, 2.09)
Enz + ADT	0.51 (0.38, 0.70)	-	0.88 (0.61, 1.27)	0.93 (0.71, 1.22)
Apa + ADT	0.58 (0.44, 0.78)	1.14 (0.79, 1.63)	-	1.06 (0.83, 1.35)
ADT	0.55 (0.48, 0.64)	1.07 (0.82, 1.40)	0.94 (0.74, 1.20)	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

Main analysis of latest trial data after unblinding

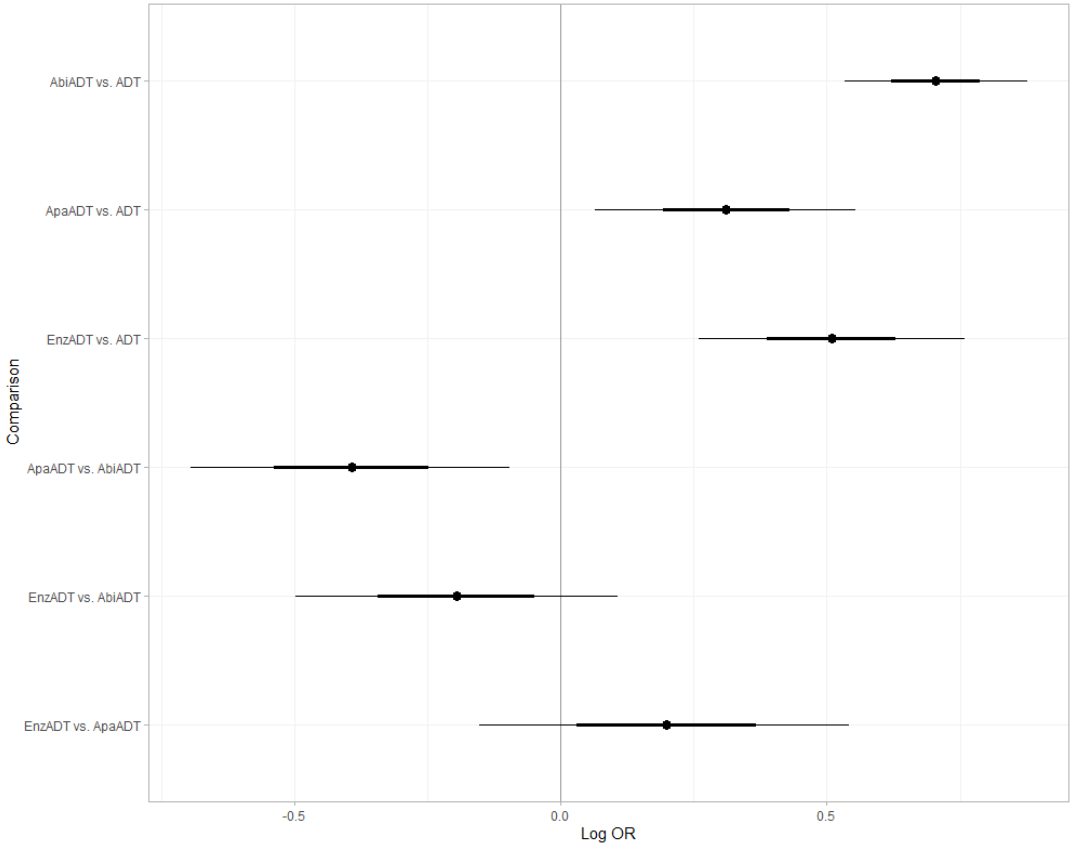
Included studies (populations):

- LATITUDE (High risk mHSPC patients)
- TITAN (All mHSPC patients)
- ARCHES (All mHSPC patients)
- STAMPEDE (All mHSPC patients)

Outcome: Odds ratio (OR) of a grade 3 or 4 adverse event

Statistical method: Fixed effect network meta-analysis

Figure 33: Forest plot of NMA Grade 3 or 4 adverse events results in terms of the logarithm of HR:



Bullets are point estimates. Regular lines are 95% credible intervals. Bold lines are point estimates ± one standard deviation.

Abbreviations: ADT, ADT only; AbiADT, Abiraterone with ADT; ApaADT, Apalutamide with ADT; EnzADT, Enzalutamide with ADT.

Table 75: Estimates of Log OR for treatment comparisons of interest:

Comparison	Log OR	sd	95% CrI of Log OR	
AbiADT vs. ADT	0.70	0.09	0.53	0.88
ApaADT vs. ADT	0.31	0.12	0.07	0.55
EnzADT vs. ADT	0.51	0.13	0.26	0.76
ApaADT vs. AbiADT	-0.39	0.15	-0.70	-0.10
EnzADT vs. AbiADT	-0.20	0.15	-0.50	0.11
EnzADT vs. ApaADT	0.20	0.18	-0.15	0.54

Abbreviations: sd, standard deviation; CrIs, credible intervals.

Table 76: Estimates of OR for grade 3 or 4 adverse events with 95% credible intervals

	Abi + ADT	**Enz + ADT**	**Apa + ADT**	**ADT**
Abi + ADT	-	1.22 (0.90, 1.65)	1.48 (1.10, 2.00)	2.02 (1.71, 2.40)
Enz + ADT	0.82 (0.61, 1.11)	-	1.22 (0.86, 1.72)	1.66 (1.30, 2.14)
Apa + ADT	0.67 (0.50, 0.91)	0.82 (0.58, 1.17)	-	1.37 (1.07, 1.74)
ADT	0.49 (0.42, 0.59)	0.60 (0.47, 0.77)	0.73 (0.57, 0.94)	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

Sensitivity check of main analysis of latest trial data up to a 40 month follow-up

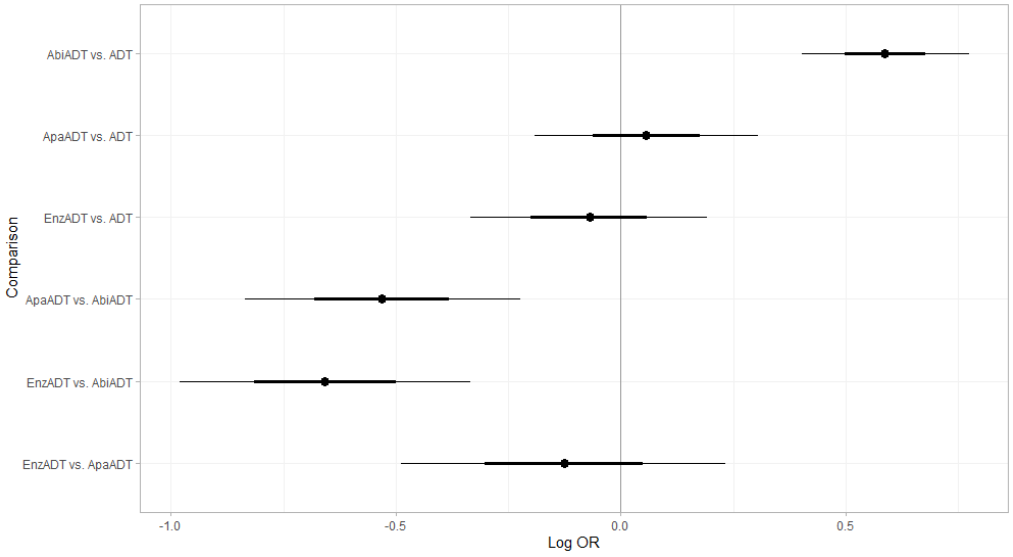
Following the methodology outlined in Section 5.2.3, a sensitivity analysis was performed of the NMA just presented for the latest trial data up to a 40 month follow-up that included trial data relating to grade 3 and 4 adverse events for all mHSPC patients in the trials of interest independent of risk classification rather than focusing on high risk mHSPC patients. It can be seen that the results of the NMA for grade 3 or 4 adverse events for the latest trial data up to a 40 month follow-up are fairly insensitive to the risk classification of the patients.

Included studies (populations):

- TITAN (people with mHSPC)
- ARCHES (people with mHSPC)
- STAMPEDE (people with mHSPC)

Outcome: Odds ratio (OR) of a grade 3 or 4 adverse event
Statistical method: Fixed effect network meta-analysis

Figure 34: Forest plot of NMA Grade 3 or 4 adverse events results in terms of the logarithm of OR:



Bullets are point estimates. Regular lines are 95% credible intervals. Bold lines are point estimates ± one standard deviation.

Abbreviations: ADT, ADT only; AbiADT, Abiraterone with ADT; ApaADT, Apalutamide with ADT; EnzADT, Enzalutamide with ADT.

Table 77: Estimates of Log OR for treatment comparisons of interest:

Comparison	Log OR	sd	95% CrIs of Log OR	
AbiADT vs. ADT	0.59	0.09	0.40	0.77
ApaADT vs. ADT	0.06	0.13	-0.19	0.30
EnzADT vs. ADT	-0.07	0.14	-0.34	0.19
ApaADT vs. AbiADT	-0.53	0.16	-0.84	-0.22
EnzADT vs. AbiADT	-0.66	0.16	-0.98	-0.33
EnzADT vs. ApaADT	-0.13	0.18	-0.49	0.23

Abbreviations: sd, standard deviation; CrIs, credible intervals.

Table 78: Estimates of OR for grade 3 or 4 adverse events with 95% credible intervals

	Abi + ADT	**Enz + ADT**	**Apa + ADT**	**ADT**
Abi + ADT	-	1.93 (1.40, 2.67)	1.70 (1.25, 2.31)	1.80 (1.50, 2.17)
Enz + ADT	0.52 (0.37, 0.72)	-	0.88 (0.61, 1.26)	0.93 (0.72, 1.21)
Apa + ADT	0.59 (0.43, 0.80)	1.14 (0.79, 1.63)	-	1.06 (0.83, 1.36)
ADT	0.56 (0.46, 0.67)	1.07 (0.82, 1.40)	0.95 (0.74, 1.21)	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

Sensitivity check of main analysis of latest trial data after unblinding

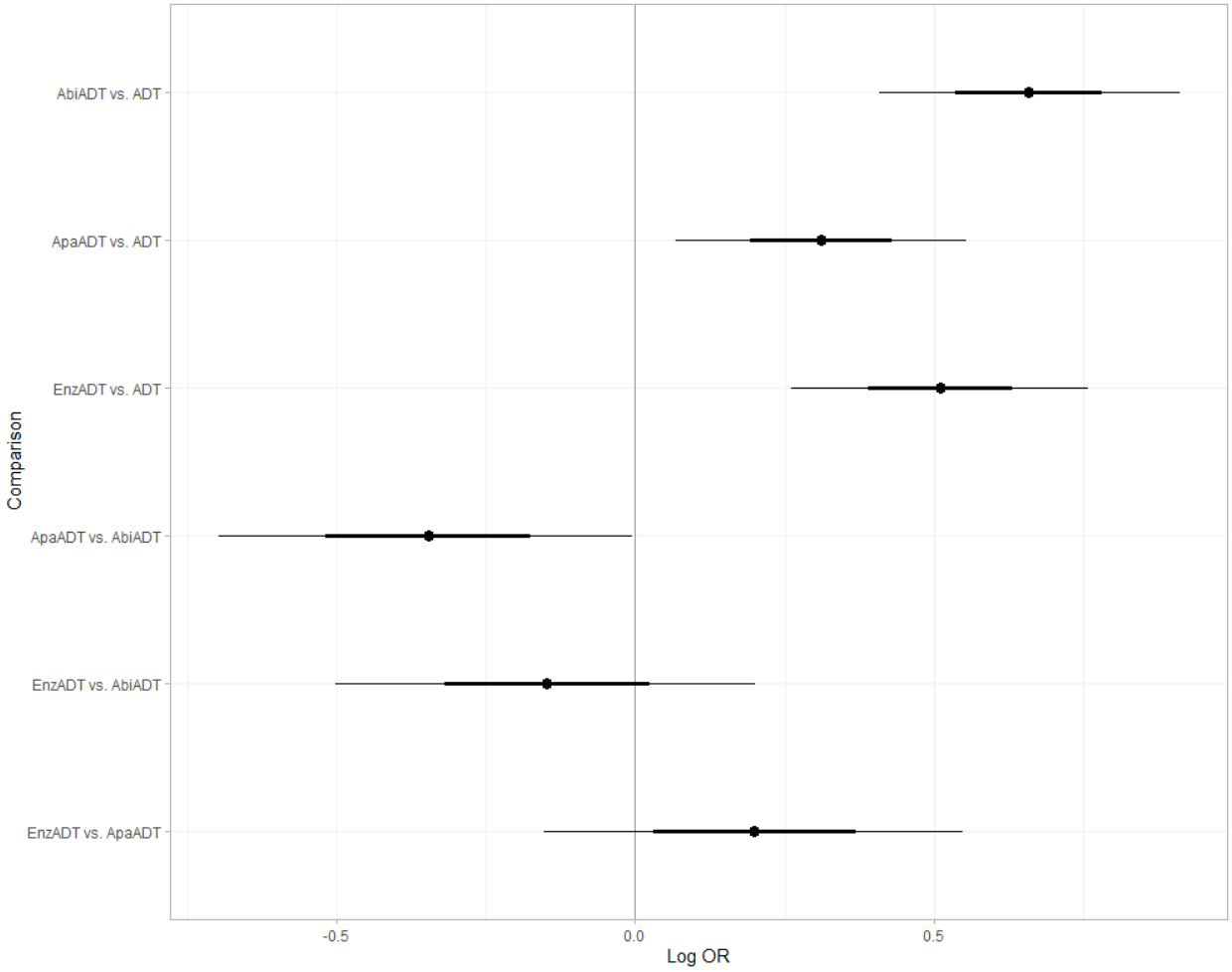
A sensitivity analysis was performed of the NMA just presented for the latest trial data after the trials concerned became open label that included trial data relating to grade 3 and 4 adverse events for all mHSPC patients in the trials of interest independent of risk classification rather than focusing on high risk mHSPC patients. It can be seen that the results of the NMA for grade 3 or 4 adverse events for the latest trial data after unblinding are not highly sensitive to the risk classification of the patients.

Included studies (populations):

- LATITUDE (People with high-risk mHSPC)
- TITAN (people with mHSPC)
- ARCHES (people with mHSPC)
- STAMPEDE (people with mHSPC)

Outcome: Odds ratio (OR) of a grade 3 or 4 adverse event
Statistical method: Fixed effect network meta-analysis

Figure 35: Forest plot of NMA Grade 3 or 4 adverse events results in terms of the logarithm of OR:



Bullets are point estimates. Regular lines are 95% credible intervals. Bold lines are point estimates ± one standard deviation.

Abbreviations: ADT, ADT only; AbiADT, Abiraterone with ADT; ApaADT, Apalutamide with ADT; EnzADT, Enzalutamide with ADT.

Table 79: Estimates of Log OR for treatment comparisons of interest:

Comparison	Log OR	sd	95% CrIs of Log OR	
AbiADT vs. ADT	0.66	0.13	0.41	0.91
ApaADT vs. ADT	0.31	0.12	0.07	0.55
EnzADT vs. ADT	0.51	0.13	0.26	0.76
ApaADT vs. AbiADT	-0.35	0.18	-0.70	0.00
EnzADT vs. AbiADT	-0.15	0.18	-0.50	0.20
EnzADT vs. ApaADT	0.20	0.18	-0.15	0.55

Abbreviations: sd, standard deviation; CrIs, credible intervals.

Table 80: Estimates of OR for grade 3 or 4 adverse events with 95% credible intervals

	Abi + ADT	**Enz + ADT**	**Apa + ADT**	**ADT**
Abi + ADT	-	1.16 (0.82, 1.65)	1.42 (1.00, 2.01)	1.93 (1.51, 2.49)
Enz + ADT	0.86 (0.61, 1.22)	-	1.22 (0.86, 1.73)	1.67 (1.30, 2.13)
Apa + ADT	0.71 (0.50, 1.00)	0.82 (0.58, 1.17)	-	1.37 (1.07, 1.74)
ADT	0.52 (0.40, 0.66)	0.60 (0.47, 0.77)	0.73 (0.57, 0.93)	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

Main analysis of latest trial data up to a 40-month follow-up

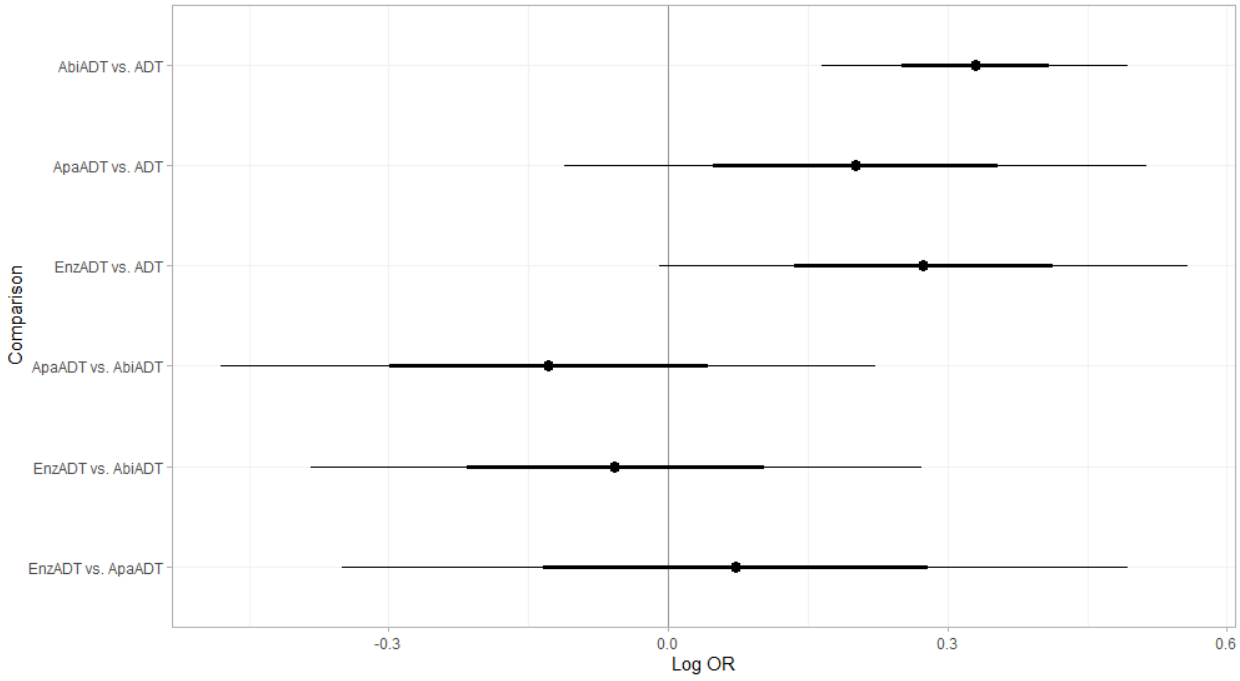
Included studies (populations):

- LATITUDE (High risk mHSPC patients)
- TITAN (All mHSPC patients)
- ARCHES (All mHSPC patients)
- STAMPEDE (All mHSPC patients)

Outcome: Odds ratio (OR) of fatigue (all grades)

Statistical method: Fixed effect network meta-analysis

Figure 36: Forest plot of NMA fatigue results in terms of the logarithm of OR:



Bullets are point estimates. Regular lines are 95% credible intervals. Bold lines are point estimates ± one standard deviation.

Abbreviations: ADT, ADT only; AbiADT, Abiraterone with ADT; ApaADT, Apalutamide with ADT; EnzADT, Enzalutamide with ADT.

Table 81: Estimates of Log OR for treatment comparisons of interest:

Comparison	Log OR	sd	95% CrI of Log OR	
AbiADT vs. ADT	0.33	0.08	0.17	0.49

Comparison	Log OR	sd	95% CrI of Log OR	
ApaADT vs. ADT	0.20	0.16	-0.11	0.51
EnzADT vs. ADT	0.27	0.14	-0.01	0.56
ApaADT vs. AbiADT	-0.13	0.18	-0.48	0.22
EnzADT vs. AbiADT	-0.06	0.17	-0.38	0.27
EnzADT vs. ApaADT	0.07	0.22	-0.35	0.49

Abbreviations: sd, standard deviation; CrIs, credible intervals.

Table 82: Estimates of OR for fatigue (all grades) with 95% credible intervals

	Abi + ADT	**Enz + ADT**	**Apa + ADT**	**ADT**
Abi + ADT	-	1.06 (0.76, 1.47)	1.14 (0.80, 1.62)	1.39 (1.18, 1.64)
Enz + ADT	0.95 (0.68, 1.31)	-	1.07 (0.70, 1.64)	1.31 (0.99, 1.75)
Apa + ADT	0.88 (0.62, 1.25)	0.93 (0.61, 1.42)	-	1.22 (0.89, 1.67)
ADT	0.72 (0.61, 0.85)	0.76 (0.57, 1.01)	0.82 (0.60, 1.12)	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

Main analysis of latest trial data after unblinding

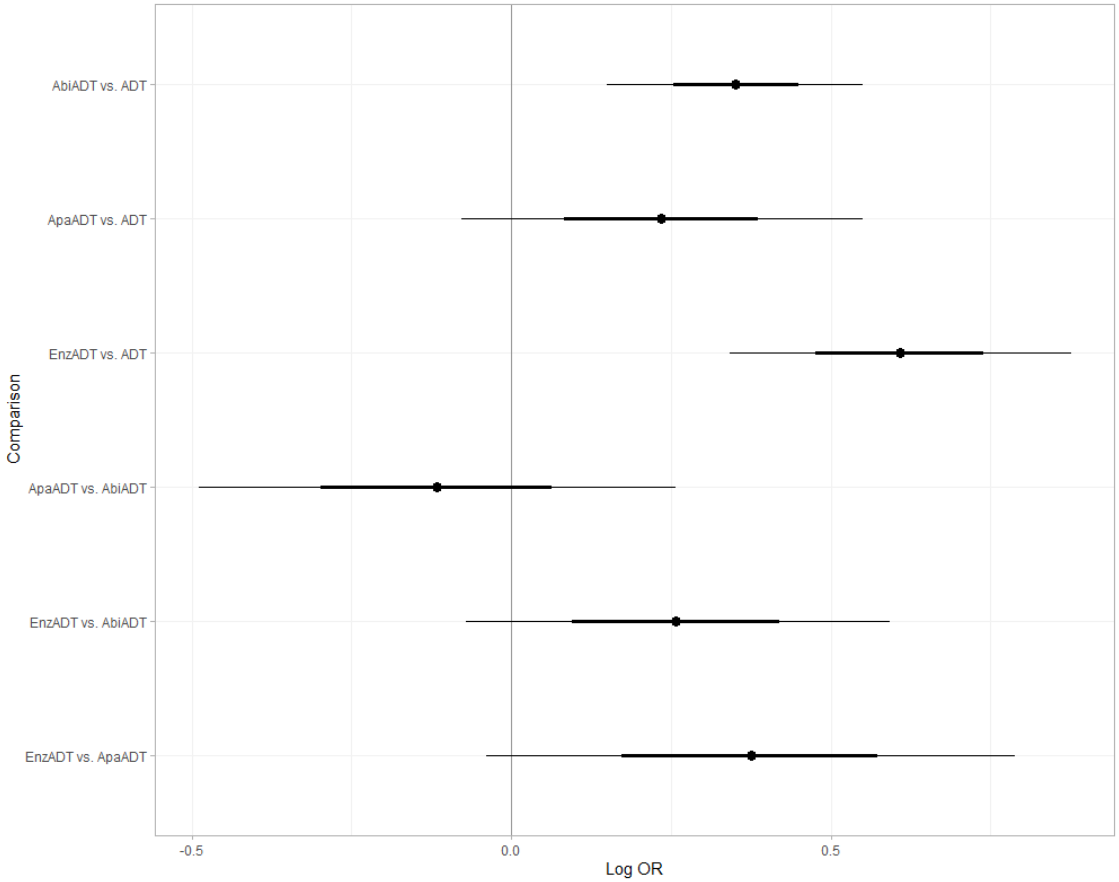
Included studies (populations):

- LATITUDE (people with high-risk mHSPC)
- TITAN (people with mHSPC)
- ARCHES (people with mHSPC)
- STAMPEDE (people with mHSPC)

Outcome: Odds ratio (OR) of fatigue (all grades)

Statistical method: Fixed effect network meta-analysis

Figure 37: Forest plot of NMA fatigue results in terms of the logarithm of OR:



Bullets are point estimates. Regular lines are 95% credible intervals. Bold lines are point estimates ± one standard deviation.

Abbreviations: ADT, ADT only; AbiADT, Abiraterone with ADT; ApaADT, Apalutamide with ADT; EnzADT, Enzalutamide with ADT.

Table 83: Estimates of Log OR for treatment comparisons of interest:

Comparison	Log OR	sd	95% CrIs of Log OR	
AbiADT vs. ADT	0.35	0.10	0.15	0.55
ApaADT vs. ADT	0.23	0.16	-0.08	0.55
EnzADT vs. ADT	0.61	0.14	0.34	0.88
ApaADT vs. AbiADT	-0.12	0.19	-0.49	0.26
EnzADT vs. AbiADT	0.26	0.17	-0.07	0.59
EnzADT vs. ApaADT	0.37	0.21	-0.04	0.79

Abbreviations: sd, standard deviation; CrIs, credible intervals.

Table 84: Estimates of OR for fatigue (all grades) with 95% credible intervals

	Abi + ADT	**Enz + ADT**	**Apa + ADT**	**ADT**
Abi + ADT	-	0.77 (0.55 1.07)	1.12 (0.77, 1.63)	1.42 (1.16, 1.73)
Enz + ADT	1.29 (0.93, 1.81)	-	1.45 (0.96, 2.20)	1.84 (1.41, 2.40)
Apa + ADT	0.89 (0.61, 1.29)	0.69 (0.45, 1.04)	-	1.26 (0.93, 1.73)
ADT	0.70 (0.58, 0.86)	0.54 (0.42, 0.71)	0.79 (0.58, 1.08)	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

Sensitivity check of main analysis of latest trial data up to a 40 month follow-up

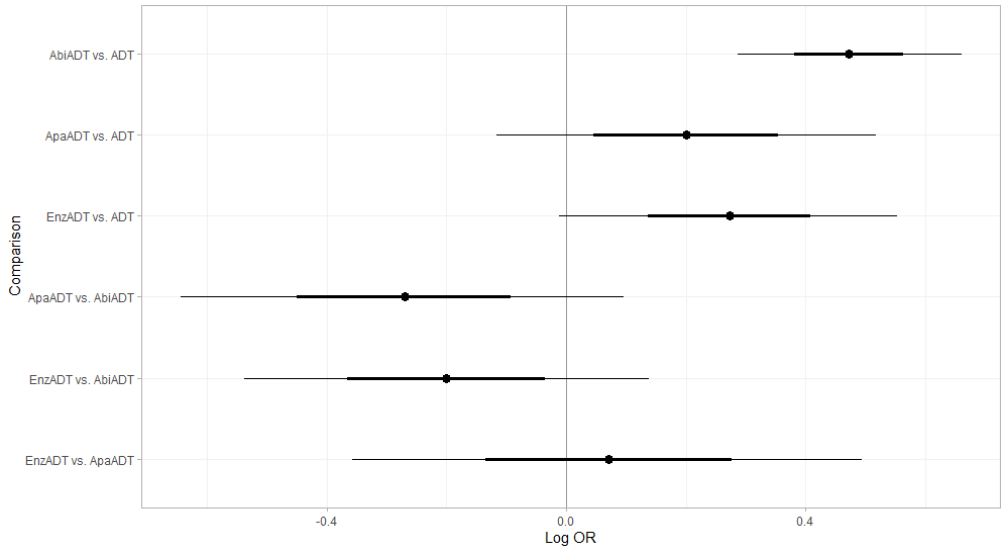
Following the methodology outlined in Section 5.2.3, a sensitivity analysis was performed of the NMA just presented for the latest trial data up to a 40 month follow-up that included trial data relating to any reported fatigue for all mHSPC patients in the trials of interest independent of risk classification rather than focusing on high risk mHSPC patients. It can be seen that the results of the NMA for any reported fatigue for the latest trial data up to a 40 month follow-up are fairly insensitive to the risk classification of the patients.

Included studies (populations):

- TITAN (People with mHSPC)
- ARCHES (People with mHSPC)
- STAMPEDE (People with mHSPC)

Outcome: Odds ratio (OR) of fatigue (all grades)
Statistical method: Fixed effect network meta-analysis

Figure 38: Forest plot of NMA fatigue results in terms of the logarithm of OR:



Bullets are point estimates. Regular lines are 95% credible intervals. Bold lines are point estimates ± one standard deviation.

Abbreviations: ADT, ADT only; AbiADT, Abiraterone with ADT; ApaADT, Apalutamide with ADT; EnzADT, Enzalutamide with ADT.

Figure 39: Estimates of Log OR for treatment comparisons of interest:

Comparison	Log OR	sd	95% CrIs of Log OR	
AbiADT vs. ADT	0.47	0.10	0.29	0.66
ApaADT vs. ADT	0.20	0.16	-0.12	0.52
EnzADT vs. ADT	0.27	0.14	-0.01	0.55
ApaADT vs. AbiADT	-0.27	0.19	-0.64	0.10
EnzADT vs. AbiADT	-0.20	0.17	-0.54	0.14
EnzADT vs. ApaADT	0.07	0.22	-0.36	0.49

Abbreviations: sd, standard deviation; CrIs, credible intervals.

Table 85: Estimates of OR for fatigue (all grades) with 95% credible intervals

	Abi + ADT	**Enz + ADT**	**Apa + ADT**	**ADT**
Abi + ADT	-	1.22 (0.87, 1.71)	1.31 (0.91, 1.91)	1.60 (1.33, 1.93)
Enz + ADT	0.82 (0.58, 1.15)	-	1.07 (0.70, 1.64)	1.31 (0.99, 1.74)
Apa + ADT	0.76 (0.52, 1.10)	0.93 (0.61, 1.43)	-	1.22 (0.89, 1.68)
ADT	0.62 (0.52, 0.75)	0.76 (0.57, 1.01)	0.82 (0.60, 1.12)	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

Sensitivity check of main analysis of latest trial data after unblinding

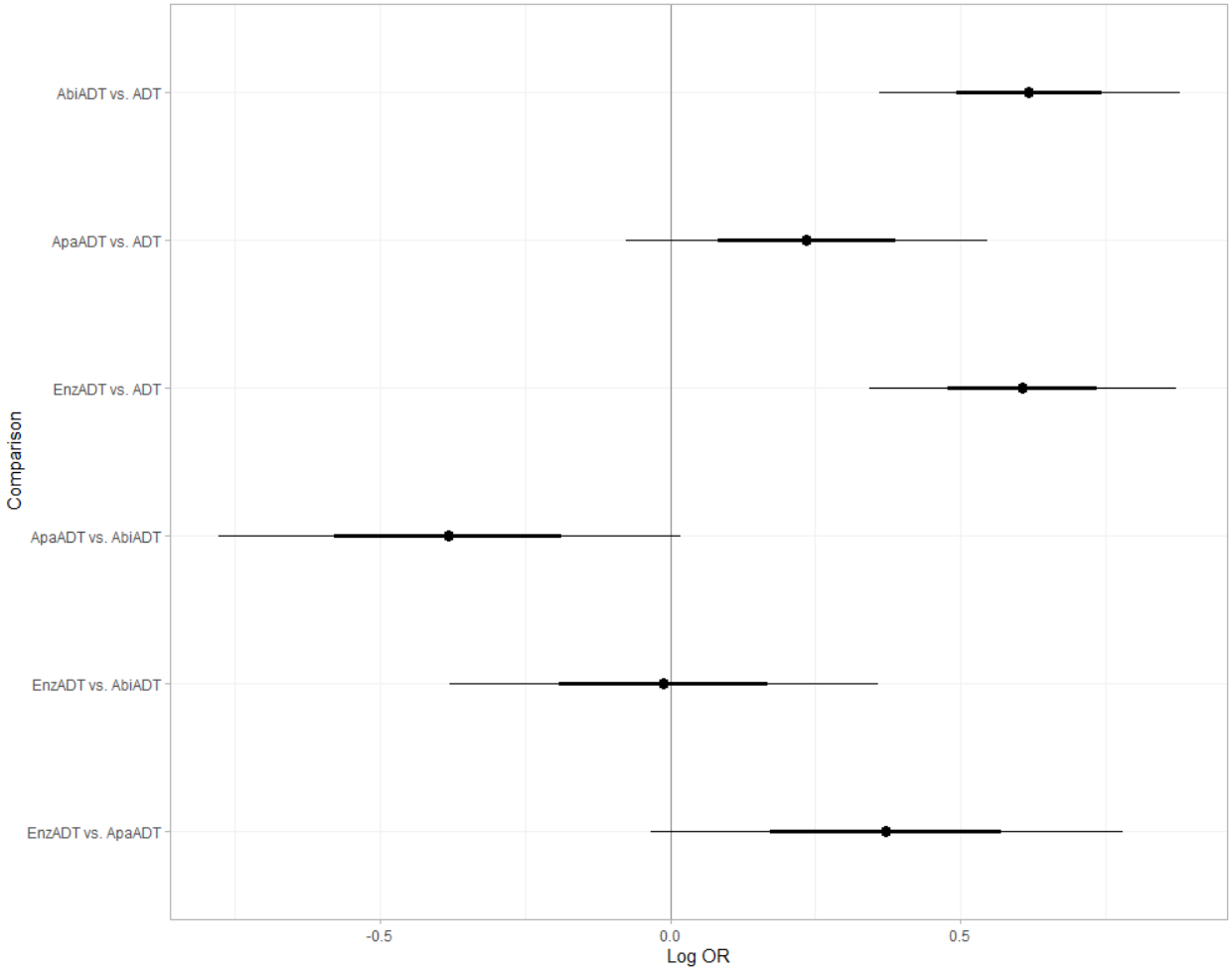
A sensitivity analysis was performed of the NMA just presented for the latest trial data after the trials concerned became open label that included trial data relating to any reported fatigue for all mHSPC patients in the trials of interest independent of risk classification rather than focusing on high risk mHSPC patients. It can be seen that the results of the NMA for any reported fatigue for the latest trial data after unblinding are not highly sensitive to the risk classification of the patients.

Included studies (populations):

- TITAN (people with mHSPC)
- ARCHES (people with mHSPC)
- STAMPEDE (people with mHSPC)

Outcome: Odds ratio (OR) of fatigue (all grades)
Statistical method: Fixed effect network meta-analysis

Figure 40: Forest plot of NMA fatigue results in terms of the logarithm of OR:



Bullets are point estimates. Regular lines are 95% credible intervals. Bold lines are point estimates ± one standard deviation.

Abbreviations: ADT, ADT only; AbiADT, Abiraterone with ADT; ApaADT, Apalutamide with ADT; EnzADT, Enzalutamide with ADT.

Table 86: Estimates of Log OR for fatigue (all grades) :

Comparison	Log OR	sd	95% CrIs of Log OR	
AbiADT vs. ADT	0.62	0.13	0.36	0.88
ApaADT vs. ADT	0.23	0.16	-0.08	0.55
EnzADT vs. ADT	0.61	0.14	0.34	0.87
ApaADT vs. AbiADT	-0.38	0.20	-0.78	0.02
EnzADT vs. AbiADT	-0.01	0.19	-0.38	0.36
EnzADT vs. ApaADT	0.37	0.21	-0.03	0.78

Abbreviations: sd, standard deviation; CrIs, credible intervals.

Table 87: Estimates of OR for fatigue (all grades) with 95% credible intervals

	Abi + ADT	**Enz + ADT**	**Apa + ADT**	**ADT**
Abi + ADT	-	1.01 (0.70, 1.46)	1.47 (0.98, 2.18)	1.85 (1.43, 2.40)
Enz + ADT	0.99 (0.68, 1.43)	-	1.45 (0.97, 2.18)	1.83 (1.41, 2.39)
Apa + ADT	0.68 (0.46, 1.02)	0.69 (0.46, 1.03)	-	1.26 (0.93, 1.73)
ADT	0.54 (0.42, 0.70)	0.55 (0.42, 0.71)	0.79 (0.58, 1.08)	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

Grade ≥ 3 Hypertension

Main analysis of latest trial data up to a 40-month follow-up

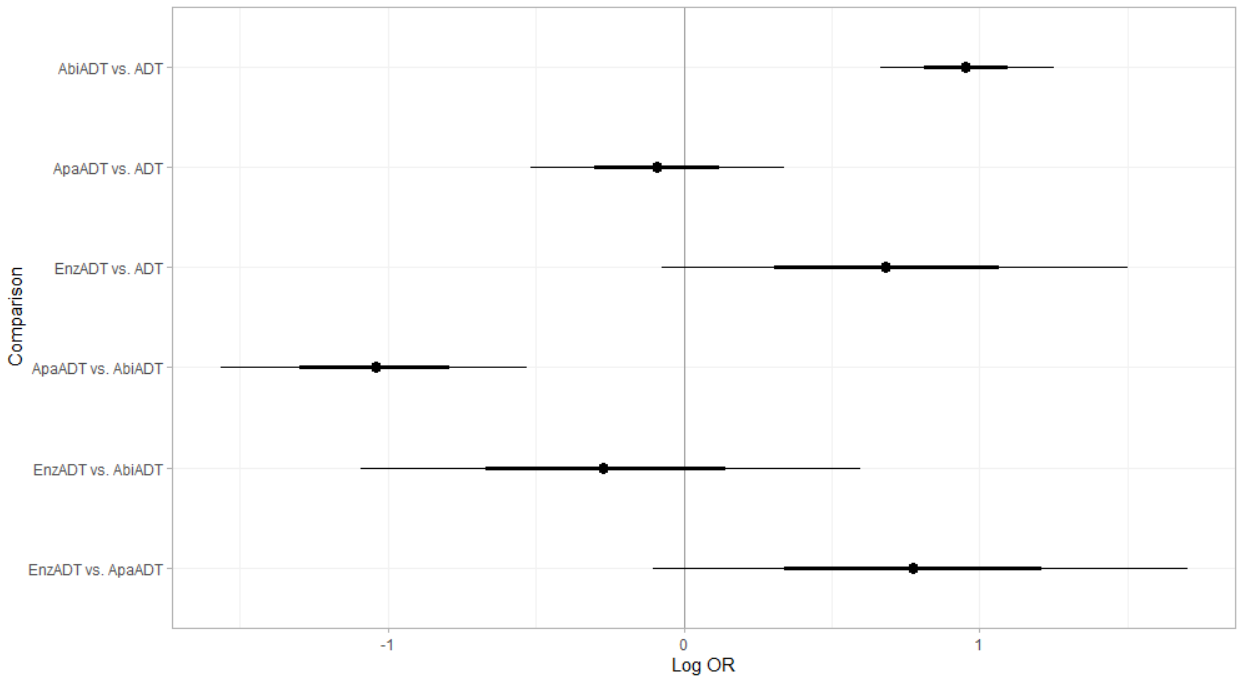
Included studies (populations):

- LATITUDE (people with high-risk mHSPC)
- TITAN (people with mHSPC)
- ARCHES (people with mHSPC)
- STAMPEDE (people with mHSPC)

Outcome: Odds ratio (OR) of grade ≥ 3 hypertension

Statistical method: Fixed effect network meta-analysis

Figure 41: Forest plot of NMA Grade ≥ 3 hypertension results in terms of the logarithm of OR:



Bullets are point estimates. Regular lines are 95% credible intervals. Bold lines are point estimates ± one standard deviation.

Abbreviations: ADT, ADT only; AbiADT, Abiraterone with ADT; ApaADT, Apalutamide with ADT; EnzADT, Enzalutamide with ADT.

Table 88: Estimates of Log OR for grade ≥ 3 hypertension

Comparison	Log OR	sd	95% CrIs of Log OR	
AbiADT vs. ADT	0.95	0.15	0.67	1.25
ApaADT vs. ADT	-0.09	0.22	-0.52	0.34
EnzADT vs. ADT	0.69	0.40	-0.08	1.50
ApaADT vs. AbiADT	-1.04	0.27	-1.57	-0.53
EnzADT vs. AbiADT	-0.27	0.43	-1.09	0.60
EnzADT vs. ApaADT	0.78	0.46	-0.10	1.70

Abbreviations: sd, standard deviation; CrIs, credible intervals.

Table 89: Estimates of OR for grade ≥ 3 hypertension with 95% credible intervals

	Abi + ADT	**Enz + ADT**	**Apa + ADT**	**ADT**
Abi + ADT	-	1.30 (0.55, 2.97)	2.84 (1.70, 4.79)	2.60 (1.94, 3.49)
Enz + ADT	0.77 (0.34, 1.82)	-	2.18 (0.90, 5.48)	1.99 (0.93, 4.48)
Apa + ADT	0.35 (0.21, 0.59)	0.46 (0.18, 1.11)	-	0.91 (0.60, 1.40)
ADT	0.38 (0.29, 0.51)	0.50 (0.22, 1.08)	1.09 (0.71, 1.68)	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

Main analysis of latest trial data after unblinding

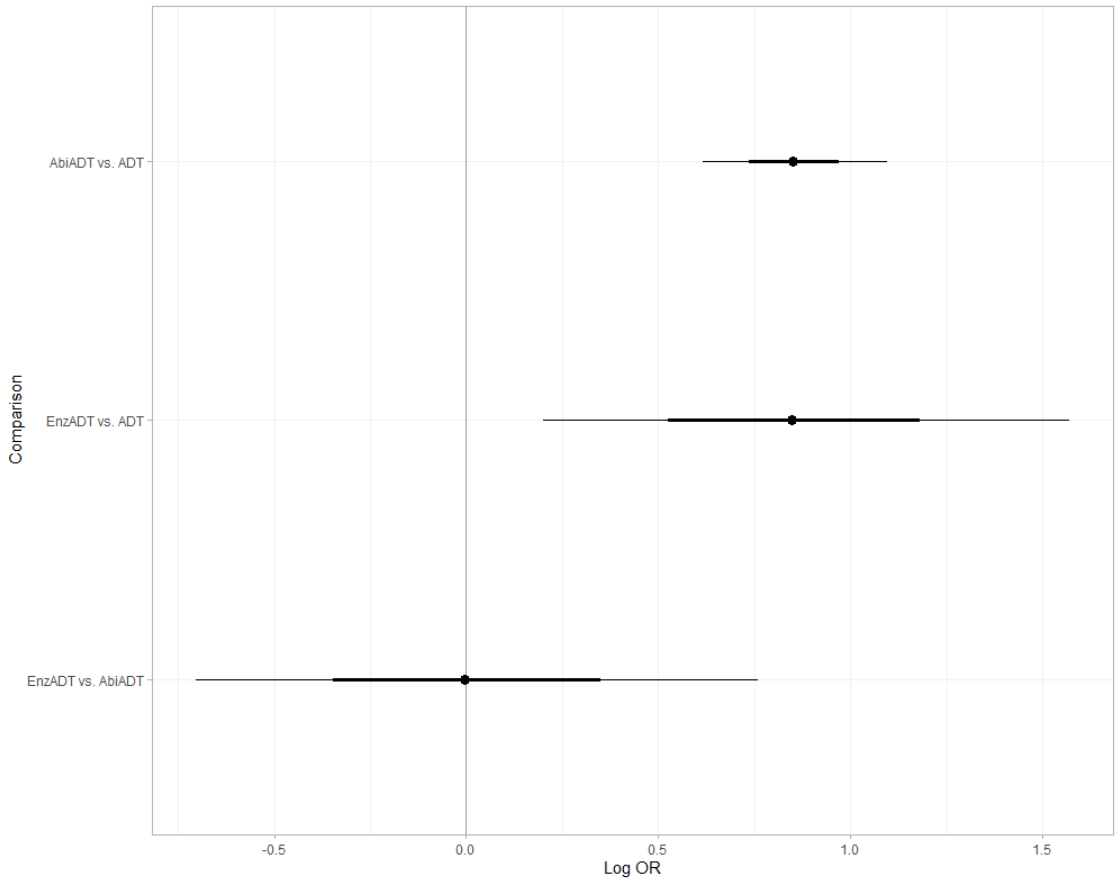
Included studies (populations):

- LATITUDE (people with high-risk mHSPC)
- ARCHES (people with mHSPC)
- STAMPEDE (people with mHSPC)

Outcome: Odds ratio (OR) of grade ≥ 3 hypertension

Statistical method: Fixed effect network meta-analysis

Figure 42: Forest plot of NMA Grade ≥ 3 hypertension results in terms of the logarithm of OR



Bullets are point estimates. Regular lines are 95% credible intervals. Bold lines are point estimates ± one standard deviation.

Abbreviations: ADT, ADT only; AbiADT, Abiraterone with ADT; ApaADT, Apalutamide with ADT; EnzADT, Enzalutamide with ADT.

Table 90: Estimates of Log OR for grade ≥ 3 hypertension

Comparison	Log OR	sd	95% CrIs of Log OR	
AbiADT vs. ADT	0.85	0.12	0.62	1.10
EnzADT vs. ADT	0.85	0.35	0.20	1.57
EnzADT vs. AbiADT	0.00	0.37	-0.70	0.76

Abbreviations: sd, standard deviation; CrIs, credible intervals.

Table 91: Estimates of OR for grade ≥ 3 hypertension with 95% credible intervals

	Abi + ADT	**Enz + ADT**	**ADT**
Abi + ADT	-	1.00 (0.47, 2.02)	2.34 (1.85, 2.99)
Enz + ADT	1.00 (0.49, 2.13)	-	2.35 (1.22, 4.81)
ADT	0.43 (0.33, 0.54)	0.43 (0.21, 0.82)	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

Sensitivity check of main analysis of latest trial data up to a 40 month follow-up

Following the methodology outlined in Section 5.2.3, a sensitivity analysis was performed of the NMA just presented for the latest trial data up to a 40 month follow-up that included trial data relating to a grade ≥ 3 hypertension assessment for all mHSPC patients in the trials of interest independent of risk classification rather than focusing on high risk mHSPC patients. It can be seen that the results of the NMA for a grade ≥ 3 hypertension assessment for the latest trial data up to a 40 month follow-up are not highly sensitive to the risk classification of the patients.

Included studies (populations):

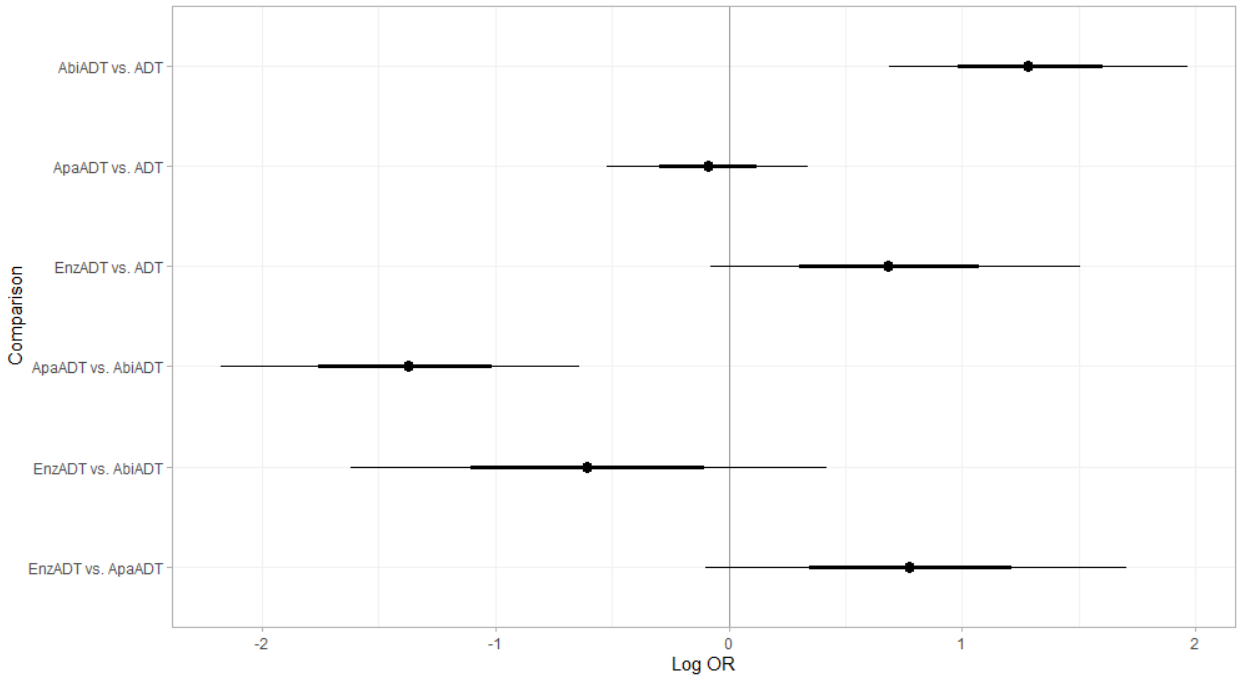
TITAN (People with mHSPC)

ARCHES (People with mHSPC), STAMPEDE (People with mHSPC)

Outcome: Odds ratio (OR) of grade ≥ 3 hypertension

Statistical method: Fixed effect network meta-analysis

Figure 43: Forest plot of NMA Grade ≥ 3 hypertension results in terms of the logarithm of OR:



Bullets are point estimates. Regular lines are 95% credible intervals. Bold lines are point estimates ± one standard deviation.

Abbreviations: ADT, ADT only; AbiADT, Abiraterone with ADT; ApaADT, Apalutamide with ADT; EnzADT, Enzalutamide with ADT.

Table 92: Estimates of Log OR for grade ≥ 3 hypertension:

Comparison	Log OR	sd	95% CrIs of Log OR	
AbiADT vs. ADT	1.29	0.33	0.68	1.96
ApaADT vs. ADT	-0.09	0.22	-0.52	0.34
EnzADT vs. ADT	0.69	0.40	-0.08	1.50
ApaADT vs. AbiADT	-1.38	0.39	-2.18	-0.64
EnzADT vs. AbiADT	-0.60	0.52	-1.62	0.42
EnzADT vs. ApaADT	0.78	0.46	-0.10	1.70

Abbreviations: sd, standard deviation; CrIs, credible intervals.

Table 93: Estimates of OR for grade ≥ 3 hypertension with 95% credible intervals

	Abi + ADT	**Enz + ADT**	**Apa + ADT**	**ADT**
Abi + ADT	-	1.83 (0.66, 5.04)	3.99 (1.89, 8.81)	3.64 (1.98, 7.12)
Enz + ADT	0.55 (0.20, 1.52)	-	2.18 (0.91, 5.48)	1.99 (0.92, 4.50)
Apa + ADT	0.25 (0.11, 0.53)	0.46 0.18 1.10	-	0.91 (0.59, 1.41)
ADT	0.27 (0.14, 0.50)	0.50 0.22 1.08	1.09 (0.71, 1.69)	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

Sensitivity check of main analysis of latest trial data after unblinding

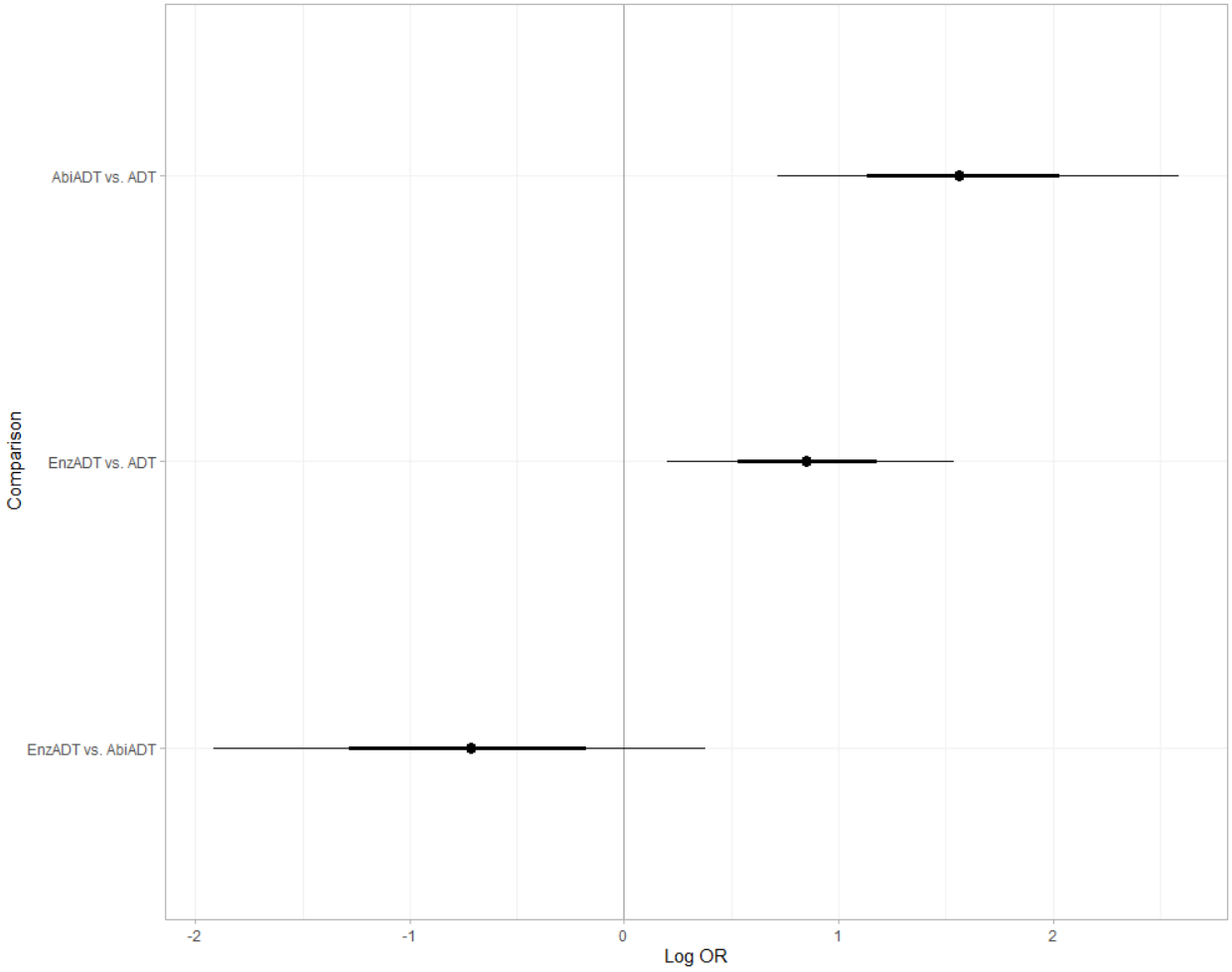
A sensitivity analysis was performed of the NMA just presented for the latest trial data after the trials concerned became open label that included trial data relating to a grade ≥ 3 hypertension assessment for all mHSPC patients in the trials of interest independent of risk classification rather than focusing on high risk mHSPC patients. It can be seen that, after taking into account the precision of the estimates of OR concerned, the results of the NMA for a grade ≥ 3 hypertension assessment for the latest trial data after unblinding are not highly sensitive to the risk classification of the patients.

Included studies (populations):

- ARCHES (people with mHSPC)
- STAMPEDE (people with mHSPC)

Outcome: Odds ratio (OR) of grade ≥ 3 hypertension
Statistical method: Fixed effect network meta-analysis

Figure 44: Forest plot of NMA Grade ≥ 3 hypertension results in terms of the logarithm of OR



Bullets are point estimates. Regular lines are 95% credible intervals. Bold lines are point estimates ± one standard deviation.

Abbreviations: ADT, ADT only; AbiADT, Abiraterone with ADT; ApaADT, Apalutamide with ADT; EnzADT, Enzalutamide with ADT.

Table 94: Estimates of Log OR for grade ≥ 3 hypertension

Comparison	Log OR	sd	95% CrIs of Log OR	
AbiADT vs. ADT	1.59	0.48	0.72	2.59
EnzADT vs. ADT	0.86	0.34	0.20	1.54
EnzADT vs. AbiADT	-0.73	0.59	-1.91	0.38

Abbreviations: sd, standard deviation; CrIs, credible intervals.

Table 95: Estimates of OR for grade ≥ 3 hypertension with 95% credible intervals

	Abi + ADT	**Enz + ADT**	**ADT**
Abi + ADT	-	2.07 (0.68, 6.79)	4.88 (2.04, 13.32)
Enz + ADT	0.48 (0.15, 1.46)	-	2.35 (1.22, 4.67)
ADT	0.20 (0.08, 0.49)	0.42 (0.21, 0.82)	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

Appendix G: comparison to other published NMAs

It was useful to compare the results of the NMA that was conducted in the present review with the results of recently published network meta-analyses of the same treatment comparisons. However, a systematic search for such NMAs conducted by the EAG found no recently published NMAs of these treatment comparisons that focused on people with high-risk mHSPC.

For this reason, the results reported in the tables below are results for the outcomes of rPFS and OS of recently published NMAs of the treatment comparisons concerned for patient sub-groups that have substantial overlap with the high risk mHSPC subgroup. This exercise was limited to the outcomes of rPFS and OS as these outcomes were identified as being the most important outcomes in conducting the present review. It should be borne in mind that the NMAs concerned included additional treatment comparisons to the ones that are of interest in the present review, which may also have affected the results of these NMAs. Nevertheless, it can be seen that the results of these NMAs for the outcomes of rPFS and OS are broadly similar to the results reported in Section 5.2.3 and Appendix F of the NMAs that the EAG conducted on the basis of both the latest trial data up to a 40 month follow-up and using the latest trial data after the trials concerned became open label.

rPFS

Table 96: Estimates of HR for rPFS with 95% credible intervals for mHSPC patients with Gleason Score ≥ 8 from the NMA published in Wang et al. (2024)

	Abi + ADT	Enz + ADT	Apa + ADT
Abi + ADT	-	1.11 (0.89, 1.37)	0.97 (0.72, 1.28)
Enz + ADT	0.90 (0.73, 1.12)	-	0.87 (0.64, 1.18)
Apa + ADT	1.03 (0.78, 1.39)	1.15 (0.85, 1.56)	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

Source: Wang et al. (2024)[13]

Table 97: Estimates of HR for rPFS with 95% credible intervals for high volume mHSPC patients from the NMA published in Jian et al. (2023)[79]

	Abi + ADT	Enz + ADT	Apa + ADT
Abi + ADT	-	1.08 (0.87, 1.33)	0.92 (0.69, 1.20)
Enz + ADT	0.93 (0.75, 1.15)	-	0.85 (0.63, 1.15)
Apa + ADT	1.09 (0.83, 1.44)	1.18 (0.87, 1.59)	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

Table 98: Estimates of HR for rPFS with 95% credible intervals for high volume mHSPC patients from the NMA published in Zhou et al. (2023)[80]

	Abi + ADT	Enz + ADT	Apa + ADT
Abi + ADT	-	1.10 (0.8, 1.52)	0.87 (0.62, 1.23)
Enz + ADT	0.91 (0.66, 1.25)	-	0.79 (0.57, 1.10)
Apa + ADT	1.15 (0.81, 1.61)		-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

Source: Zhou et al. (2023)[80]

OS

Table 99: Estimates of HR for OS with 95% credible intervals for mHSPC patients with Gleason Score ≥ 8 from the NMA published in Wang et al. (2024)

	Abi + ADT	Enz + ADT	Apa + ADT
Abi + ADT	-	0.95 (0.76, 1.18)	1.00 (0.76, 1.32)
Enz + ADT	1.05 (0.85, 1.32)	-	1.05 (0.78, 1.41)
Apa + ADT	1.00 (0.76, 1.31)	0.95 (0.71, 1.28)	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

Source: Wang et al. (2024)[13]

Table 100: Estimates of HR for OS with 95% credible intervals for high volume mHSPC patients from the NMA published in Jian et al. (2023)

	Abi + ADT	Enz + ADT	Apa + ADT
Abi + ADT	-	0.92 (0.75, 1.16)	0.94 (0.73, 1.20)
Enz + ADT	1.08 (0.86, 1.33)	-	1.01 (0.75, 1.35)
Apa + ADT	1.06 (0.83, 1.37)	0.99 (0.74,	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

Source: Jian et al. (2023)[79]

Table 101: Estimates of HR for OS with 95% cEstimates of HR for OS with 95% credible intervals for high volume mHSPC patients from the NMA published in Zhou et al. (2023)

	Abi + ADT	Enz + ADT	Apa + ADT
Abi + ADT	-	0.94 (0.73, 1.20)	0.87 (0.66, 1.14)
Enz + ADT	1.06 (0.83, 1.37)	-	0.93 (0.68, 1.27)
Apa + ADT	1.15 (0.88, 1.52)	1.08 (0.79, 1.47)	-

Abbreviations: ADT, Androgen deprivation therapy; Apa, Apalutamide; Abi, Abiraterone and prednisolone; Enz, Enzalutamide

Note: The comparison is the row-forming treatment against the column-forming treatment.

Zhou et al. (2023)[80]